Official Journal of the Interstate Postgraduate Medical Association

Volume 23, Number 5 **MAY 1958**

Postgraduate Medicine

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Special Issue

University of Minnesota Medical School

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Postgraduate Medicine

Volume 23 · Number 5

MAY · 1958

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

TABLE *of* CONTENTS

University of Minnesota Medical School Issue

GUEST EDITOR: *Robert B. Howard, M.D.*

INTRODUCTION 458

Cerebrovascular Disease in General Practice
A. IANNONE, M.D. AND A. B. BAKER, M.D. 460

A Critique of Operations for Peptic Ulcer
OWEN H. WANGENSTEEN, M.D. 466

Tranquilizing and Related Drugs; a Guide for the General Physician
BURTRUM C. SCHIELE, M.D. AND WILBUR BENSON, M.D. 484

Clinical Applications of Radioisotopes
ELMER C. PAULSON, M.D. AND DONN G. MOSSER, M.D. 493

The Chemical Basis of Radiation Damage
WALLACE D. ARMSTRONG, M.D. 499

Sarcoidosis
HENRY E. MICHELSON, M.D. 508

Discography
HAROLD O. PETERSON, M.D. 512

(Continued on page A-4)

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Fundamentals of the Scoliosis Problem for the General Practitioner
JOHN H. MOE, M.D. 518

Studies of Cardiac Output During the Early Phase of Rehabilitation
FREDERIC J. KOTTKE, M.D., WILLIAM G. KUBICEK, PH.D.,
JEAN N. DANZ, B.S. AND MILDRED E. OLSON, B.S. 533

Shock—With Particular Reference to Endotoxin Shock
MAURICE B. VISSCHER, M.D. 545

Dysproteinemia
HORACE H. ZINNEMAN, M.D. 550

Design and Clinical Application of the Helix Reservoir Pump-Oxygenator System for Extracorporeal Circulation
C. WALTON LILLEHEI, M.D. AND RICHARD A. DE WALL, M.D. 561

DEPARTMENTS

"PLACEBO"—Jackson A. Smith, M.D. A-18

YOUR QUESTIONS ANSWERED A-22

Heart Disease and Drug Addiction
Measuring Cerebral Edema
Thromboangiitis Obliterans
Intraspinal Metastasis
Iliac Index
Reaction to Penicillin

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32-33

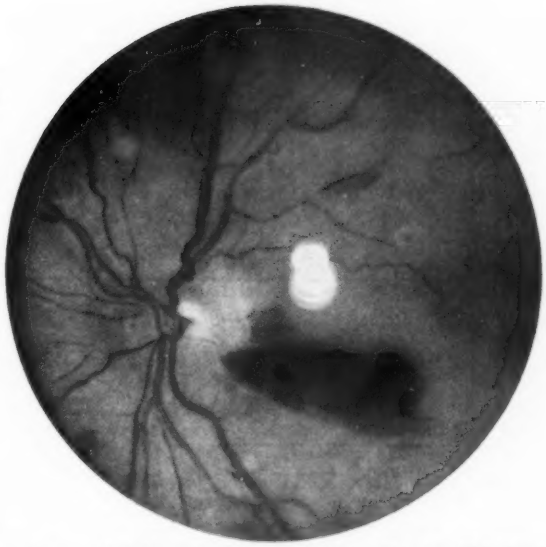
FORENSIC MEDICINE A-36
Divergent Sexuality and Criminal Behavior
JAMES M. REINHARDT, PH.D.

NEWS OF INTERSTATE A-66

(Continued on page A-6)

WHEN BLOOD PRESSURE MUST COME DOWN

AS IN THIS CASE[1]: Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.



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1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957. 2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

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LABORATORY NOTES. Arthur H. Sanford, M.D. A-68

MEDICINE FROM ABROAD A-76

CLEVELAND ASSEMBLY PROGRAM—INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION A-88

NEW FOR YOUR ARMAMENTARIUM A-112

PRODUCTS BY THERAPY INDICATIONS A-119

THE MEDICAL BOOKMAN A-130

FINANCIAL PLANNING FOR THE PRACTICING PHYSICIAN
J. K. Lasser Institute ..... Facing A-138-139

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-172

INDEX TO TECHNICAL EXHIBITS A-183

Information for AUTHORS

► POSTGRADUATE MEDICINE, the official journal of the Interstate Postgraduate Medical Association, is published to present authoritative, original articles of high scientific value and of special clinical interest, with the emphasis on diagnosis and treatment.

The Editors of POSTGRADUATE MEDICINE will be pleased to consider *original papers* in the fields of general medicine, as well as all the specialties, so presented as to be of value to practicing physicians.

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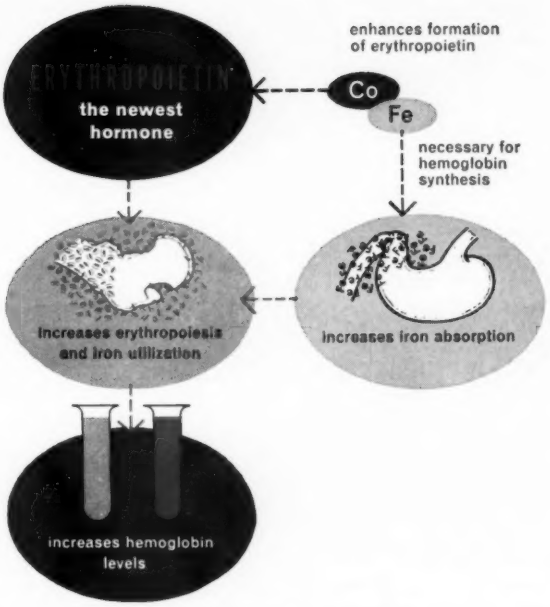
NEW RESEARCH ON ERYTHROPOIETIN EXPLAINS CLINICAL SUPERIORITY OF



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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• HEART DISEASE AND DRUG ADDICTION

Q. The patient is a 47 year old man who has had heart disease for the past 14 years. Seven years ago he was hospitalized for two months with what appeared to be a coronary occlusion; on November 25, 1957, coronary insufficiency developed. He has had severe substernal pains every night with profuse sweating, and has obtained relief only by using morphine, as both codeine and Darvon make him sick. Is there any danger of his becoming an addict from taking one dose of morphine nightly? What treatment do you suggest for the perspiration and pain?

M.D.—Michigan

A. There is a very definite chance that this man will become an addict if he takes morphine every night. The most commonly recommended coronary dilator at present is PERITRATE®, 20 mg. four times a day. NITROGLYN®, in doses of 0.1 gr. taken at 8 P.M., also has helped nocturnal angina in about 30 per cent of patients with coronary insufficiency.

• MEASURING CEREBRAL EDEMA

Q. Can you give me any information on measuring cerebral edema in humans? This term is often used in describing symptoms and signs attributable to "cerebral and corporal edema," and I have also used it in attempting to explain some of the manifestations of premenstrual tension.

M.D.—New York

A. Measuring cerebral edema in humans is quite unsatisfactory, and the balance between intracellular and extracellular tissue fluid, while it is undoubtedly altered pathologically, particularly in cases of cerebral trauma, has given rise to no precise measurements.

The most striking instances of cerebral edema are found in infections of the nervous system, acute generalized infections, trauma and certain intoxications, mostly alcoholic. These brains are "dry" when removed at autopsy, indicating that the normal fluid spaces have been obliterated due to swelling of the brain. The clinical status of such individuals is characterized by coma. There is at present no demonstrable relationship between cerebral edema and premenstrual tension. The use of hypertonic solutions which reduce at least temporarily the intracranial pressure has not been markedly successful in relief of premenstrual tension.

• THROMBOANGIITIS OBLITERANS

Q. My patient is an identical twin of a 32 year old Caucasian woman who has thromboangiitis obliterans. What likelihood, percentagewise, is there that my patient will have the disease?

M.D.—Pennsylvania

A. A group of physicians interested particularly in vascular diseases have observed only one instance in which identical twins had thromboangiitis obliterans. No conclusions can be drawn from this observation, and no figures can be given concerning the possibility that thromboangiitis obliterans will develop in the twin sister of a patient with this condition. Incidentally, thromboangiitis obliterans occurs very infrequently in women.

(Continued on page A-24)

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*Reports to the Squibb Institute for Medical Research

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Intramuscular route—5 to 15 mg. for therapy or prophylaxis
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• INTRASPINAL METASTASIS

Q. About six years ago a 56 year old patient had a radical mastectomy, and four years later, a resection of the fifth and sixth ribs anteriorly because the disease recurred in the soft tissue. Paraplegia of sudden onset has now developed. Three days after symptoms began, she was completely paralyzed with loss of bladder and bowel function. According to a consulting neurologist, the lesion was probably due to intraspinal metastasis at the T5 level. Spinal fluid dynamics showed a complete block and proteins 760 (*sic*). X-rays of the spine showed loss of transverse process at T5. She has been taking 5 mg. of diethylstilbestrol three times a day.

What would be the proper management of bowel function? Would radiation to the spine be of any benefit? If so, how much radiation will be effective without danger to the esophagus? Has there been a case in which motor function was recovered after radiation?

M.D.—Puerto Rico

A. When involvement of the intraspinal space is present, associated with a malignant process, and the signs of damage to the spinal cord come on as rapidly as they have in this instance, it ordinarily means that the malignant process has produced the myelopathy by interrupting the vascular supply to the spinal cord. In such instances, a marked degree of recovery is uncommon after irradiation or surgical decompression. If the onset of the signs of compression of the spinal cord is slow, taking place over many days or weeks, considerable recovery may follow treatment.

In patients who have paralysis of the sphincter ani, some symptomatic benefit may be obtained by administering agents that produce a certain degree of constipation which is treated with enemas at routine intervals.

• ILIAC INDEX

Q. What is meant by the iliac index? How is it measured and what is its significance?

M.D.—Ohio

A. The iliac index is a mathematical expression of the usual reduction in acetabular or iliac angles or both in young infants afflicted with mongolism. These small angles result from the disturbed pelvic morphology which is characteristic of this condition. The iliac index is obtained by dividing by two the sum of both acetabular angles plus the sum of both iliac angles.

Further details may be found in the article by John Caffey, M.D. and Steven Ross, M.D., "Mongolism (mongoloid deficiency) during early infancy—some newly recognized diagnostic changes in the pelvic bones," which appeared in the May 1956 issue of *Pediatrics*, page 642.

• REACTION TO PENICILLIN

Q. A three year old child has had three or four attacks of adenitis and tonsillitis, with a temperature ranging up to 105° F. He responded dramatically to injections of penicillin. When oral penicillin was administered after the injections, soft stools were noted. For this reason, therapy was discontinued after three or four days. The last attack occurred about two months after the previous one, and again penicillin was indicated. Accordingly, 450,000 units of DEPO®-PENICILLIN was given, and all symptoms subsided the following day. At this time, 4,800,000 units of BICILLIN® was administered, and the next day the child had tenderness, swelling and pain with considerable fever at the site of the first injection.

Does this reaction contraindicate the future use of penicillin?

M.D.—Virginia

A. The reaction as described does not contraindicate the future use of penicillin. Sensitivity to this drug usually is manifested by a generalized reaction, with urticaria or irritative dermatitis. The fact that the child had a severe local reaction suggests that the site of injection or the vehicle was to blame, rather than the penicillin.

If another attack of tonsillitis occurs in this patient, swabbings from the throat should be obtained for culture, and studies of the sensitivity of the organism to penicillin should be carried out before drug therapy is begun. If it is necessary to use penicillin, then oral doses of the penicillin V type of preparation will assure adequate concentrations in the blood, and also will greatly diminish the possibility of severe reactions. There seems to be little need for massive intramuscular doses of the drug except in the presence of bacteremia. Any child with streptococcal tonsillitis or recurrent attacks of bacterial tonsillitis with adenitis probably should undergo tonsillectomy and adenoidectomy.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

ALCOHOLISM-LIVER TIE WEAKENED

Clinical conference, Chicago Medical Society:

• Modern medical concepts indicate that association of cirrhosis of the liver and alcoholism accounts for a relatively smaller percentage of cases than was originally suspected. Cirrhosis can strike with almost equal frequency individuals who partake of alcohol rarely or not at all. Modern therapy, designed to support the liver, includes prolonged rest, a diet rich in protein, and reduced production of toxins to lighten the detoxication load on the liver. Surgery to relieve portal hypertension, though delicate to perform, can be done with relative safety.—Dr. Arthur H. Blakemore, Columbia University College of Physicians and Surgeons, New York.

• A 36 per cent operative mortality reduction in diverticulitis was recorded at the University of Alberta Hospital between 1948 and 1957. The increasing safety justifies recommending operation for patients without advanced complications.—Dr. Walter C. MacKenzie, University of Alberta Faculty of Medicine, Edmonton.

• Initial attacks of rheumatic fever can be prevented by proper diagnosis of and therapy for streptococcal pharyngitis. More frequent use of throat cultures is necessary for diagnosis. To prevent rheumatic fever, treating a properly diagnosed streptococcal pharyngitis requires that penicillin be present in the tissues for at least 10 days.—Dr. Gene H. Stollerman, Northwestern University Medical School, Chicago.

BABY'S FIRST BREATH

The first complete scientific record of a baby's first breath has been obtained in research seeking a better understanding of respiratory malfunction. Recordings of pressures within the chest of infants during and after delivery and rapid serial x-rays of the lungs before and during the first few breaths suggest that sudden expansion of lung capillaries may assist in the first breath. The popular theory of chest recoil following the "squeeze" of delivery did not seem to play a role in lung expansion. Sudden capillary expansion may be related to changes occurring when blood flow through the umbilical cord is suddenly cut off.—Dr. Forrest H. Adams, University of California School of Medicine, Los Angeles.

DEFORMITIES LINKED TO VITAMIN A EXCESS

Thirty-sixth annual meeting, International Association for Dental Research:

• A syndrome of dentofacial anomalies resulted from abnormally high vitamin A intake during certain critical periods of pregnancy in rats. Deformities included cleft palate, malocclusion, defects in development of the bony orbit, and extreme exophthalmos.

NEW DIAGNOSTIC BLOOD TEST STUDIED

Clinical, field and laboratory studies of children with certain chronic diseases, and of their families, would seem to indicate that serum mucoids are sensitive indicators of clinical and subclinical manifestations. A method for the fractionation of serum mucoids has been developed. Many chronic diseases appear to show abnormal serum mucoid patterns which, on the basis of preliminary and limited data, seem to be characteristic for given diseases.—Dr. Winston Price, The Johns Hopkins Hospital, Baltimore.

POLIO VACCINE IMMUNITY DURATION FAVORABLE

Thirty-ninth annual session, American College of Physicians:

- Duration of immunity following administration of a killed-virus vaccine for poliomyelitis can be determined only with the passage of time; however, current observations can give some indication of trend. Evidence deduced thus far seems to support the hypothesis that immunity to paralysis is active not only if serum antibody is present at the time of infection but also if the immunologic mechanism is sufficiently hyperreactive to respond with the formation of sufficient antibodies to intercept invasion of the central nervous system, even though infection at the portal of entry does occur. There is reason to believe that the formation of high concentrations of antibodies may have an ameliorating effect, even after central nervous system invasion.—Dr. Jonas E. Salk, University of Pittsburgh School of Medicine.

- During the past epidemic of Asian influenza in this country, which reached the New Orleans area first, the electrocardiograms and, to some extent, the vectorcardiograms of a number of patients showed alteration. Some injury to the myocardium, which apparently was related to the epidemic, developed in certain patients.—Dr. George E. Burch, Jr., Tulane University School of Medicine, New Orleans.

- The current problem of hospital-acquired, antibiotic-resistant staphylococcal infections is nowhere more apparent than in hospital maternity units. The number of extensive outbreaks involving large groups of infants with localized and systemic infections and mothers with breast abscesses has increased steadily in recent years. In practically all instances of the more than 70 outbreaks in the United States and abroad studied (at Ohio State College of Medicine), the etiologic agent has been *Staphylococcus pyogenes*, bacteriophage type 42B/80/81.—Dr. Thomas E. Shaffer, professor of pediatrics, Ohio State University College of Medicine, Columbus.

AREA HOSPITALS

Thirteenth National Conference on Rural Health:

- Area hospitals of 100 to 200 beds, located on the basis of accessibility to a scattered population, can bring better medical care to rural people. Highly qualified specialists would be attracted because the hospitals would give them the necessary patient volume to make the move economically feasible.—Dr. F. J. L. Blasingame, general manager, American Medical Association.

QUESTIONS "TERMINAL" CANCER TESTS

Testing potentially useful anticancer drugs in patients in the terminal stage of the disease may not be a fair standard. Patients seriously ill with heart disease, it is recalled, do not respond to drugs which are of established value when used before the disease has progressed to the final stages.—Dr. Louis Lasagna, The Johns Hopkins University, Baltimore, before New York Academy of Sciences, New York.

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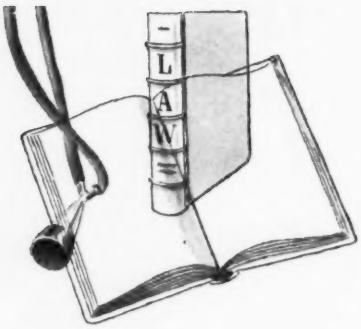

Forensic Medicine

Divergent Sexuality and Criminal Behavior

JAMES M. REINHARDT*

University of Nebraska, Lincoln

IT is a mistake to assume that one can define sexual perversions comprehensively on the basis of some classifiable deviations from a culturally recognized standard or norm of sexual behavior. All such norms are highly theoretical, idealistic norms. They are coercive, and are not the final arbiters of sexual behavior in what I now believe to be a fairly representative connubial bed in America.

JAMES M. REINHARDT

Marital Conflict Arising From Aberrant Sexual Practices

When an irreconcilable conflict develops, as when a wife rejects the deviatory sexual advances of her husband for religious or aesthetic reasons, he may find an outlet away from home. Such clandestine reprieves often invite and intensify a variety of tensions: feelings of guilt, morbid disgust, worries about job security, an increasing necessity for rationalization and explanation. These unhappy effects often are attributed to a sexually diffusive idiosyncrasy of the husband, yet such anxieties are rare in an agreeably reciprocal relationship. The psychic products and consequent growing family tensions resulting from sexual conflict tend to drain away the capacity to meet the demands of life and correspondingly multiply the burdens that must be borne.

Fortunately, it appears that more often a mutually happy adjustment is found in these unidealized forms of forepleasure histrionics. I am speaking now not of perversions at all but of harmless excursive sexual interplays not too unlike what one might observe in a couple of uninhibited monkeys.

Knowledge of the varieties and extent of mutually shared conjunctions, positions and erotic movements adhibited in a single sexual engagement probably would overwhelm one whose sexual knowledge has never crossed the boundaries of the "mythical ideal." These

(Continued on page A-38)

*Professor of Criminology, University of Nebraska, Lincoln, Nebraska.

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1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956.

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variable states of sexual excitation may go on for half an hour or more. Interestingly enough, in such instances of multiple and prolonged sexual behavior the female is more often than not the patient disciplinarian. As suggested already, this anomalous behavior is far more widespread than is generally believed. The actors are not ordinarily criminals. When a criminal shows up among them, as sometimes happens, it is not easy to find a causal relation between the criminality and the unconventional sexuality per se.

These people are not sexual perverts in any consistently logical sense of the term. They are interested in sex. The 24 compatible couples whom I studied in detail were attached emotionally to normal sex objects. There were no substitutions for that object and they all wanted to finish in the biologically idealized position. Approximately half of the 24 couples (in 10 instances the husband spoke for both) thought their own eroticisms quite normal with respect to the behavior of their married friends; the others either "didn't know" or "never discussed the matter." At least 10 of the 14 women studied were sensitive, altruistic and gave themselves normally or zealously to the promotion of human happiness both in and out of bed. One later became widowed and suffered a great deal. She tried sexual relations unsatisfactorily with two other men after her husband died, and was afraid of a second marriage.

Of the 24 couples, 38 individuals were interviewed, and all were or had been accommodatively situated. They were certainly as favorably balanced morally and aesthetically on the side of law and order as are the average unsuspected individuals on the street. They were able to employ, with delight, other interests. This is not always the case. As I have suggested, tensions within the marital relation arising from failure to harmonize modes of sexual gratification often lead to suspicions that may have tragic consequences. The member of the union whose derivative approaches are rejected may eventually become absorbed in aberrant moods and find release in veritable sex orgies. Prolonged rejection may lead

(Continued on page A-40)

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*Reiwa, D.; Clark, F.; Jennings, M.; Pullen, V.; Olson, H.; Wall, L. and Tyler, E. T.: West J. Surg. 64:152, 1956.

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to morbid fantasies that give rise to neurosis or criminal tendencies.

A number of such persons have come to me for counsel. Not infrequently both husband and wife come together. The wife is generally convinced that her husband is "sick," that he is a pervert and needs "medical care." As often as not, the husband agrees, or admits at least that he needs help. He does.

I have come upon a considerable number of penitentiary inmates with such unhappy histories of marital conflict. Most of them were inhibited men with no reserve capacity for conjugal love and loyalty, independent of an unyielding necessity for erotic expression. Some of them had been criminals before marriage; others would likely have become criminals regardless of the marital conflict. Nevertheless the sexual conflict was a provocative and complicating factor. One of these men had lived a respectable, unreproachable life until, as he put it, "That *bed*-rock drove me to drink."

Secondary Sexual Stimulants

Examination of various cultures of the world shows that each has its approved modes of sexual stimulation. The stimulators, unassociated with the conditioning effect, may bear little or no relation to the sexual act. While the normal Westerner, accustomed to different sexual patterns, abhors the strange eroticisms observed in the preliterate cultures, let him reflect for a moment on earrings, lipstick and mascara among the women of his own time and place.[1] "I remember when young girls used to spend torturous hours burning holes through their ears with knitting needles so that they could wear large earrings. And for what? Old man Dill, who never heard of Freud, told how he fell in love with Lydia's earrings and how he insisted that she wear them to bed.

"Ear ornaments and decorative forms, the world over, have tended to focus attention on some part of the body as a secondary sexual attraction. So long as these attractions remain secondary stimulants, and do not become substitute or symbolic gratifiers, they do not fall within my definition of *perversions*. They do not always remain secondary, however."[1] Whether or not they involve the individual in conflict with the law depends on individual sensitivity, unique situation, social pressure, and the availability of legitimate escape avenues. As Havelock Ellis has stated, "It may well be that the insensitive and average man never notices such details, but to the man who loves with *fantasy* and rapt attention these susceptibilities become a definite center of gravitation in the highly complex constellation of his passionate feelings."

Excessive Sexual Desires

I reported elsewhere[2] the case of a man whose sexual craving demanded intercourse more or less regularly three or four times daily. This man was intelligent, his modes of sexual satisfaction were normal, and he was financially able to accommodate his extravagant desires without conflict with the law. What might have happened if he had been confined within the walls of a penitentiary for a prolonged period, we can only guess. He might have acquired ungovernable homosexual proclivities. In isolation his imagination might well have learned to play upon the strange and morbid fantasies that over and again have impelled to sadistic cruelties, pyromania or murder. Reared in the confines of a small rural village culture, he might have been "an unembellished keeper of bees—the father of nine children." The talk of the town might well have been his wife's "schoolgirl complexion." Beyond that he might have been simply "Neighbor Brown."[2]

The "Clitorid" Female

Let me turn briefly to a type of female described by Maeder as "the clitorid type." "From her first love onward," says Maeder, "she knows no satisfaction greater than sexual enjoyment." She seeks and attracts the attention of males, soon acquires the appropriate glances and gestures to catch her man, but usually tires of him and seeks another in a short while. This type sometimes will accept two or three or four different men in marriage, depending somewhat on her ability to secure

(Continued on page A-42)

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divorces. Others of this type put up the outward appearance of modesty and familial interest while at the same time they carry on a succession of extramarital love affairs. Hemmed in by rigid family ties and closely knit community gossip, such a woman sometimes will throw overboard all pretenses with little embarrassment. Others, unable to bring themselves to the point of passing the threshold of "respectability," develop neuroses and sometimes cause endless worries before they are sent to a mental institution or sue for divorce on grounds of incompatibility.

I am not speaking here of the normal woman who becomes restless in a dry climate, of a husband who talks about the stock market in bed, and whose most romantic moment was when he put his arm around the elevator girl at the Elk's Club.

I have had occasion to observe at some length a small number of these relatively rare libidinous types. They become restless in the confines of conventionality. They often wander about seeking new loves. They sometimes sit in one jail after another. They may end up in reformatories or mental hospitals. They sometimes become thieves, kleptomaniacs or forgers. Such persons, as Maeder points out, suffer both pain and exultation because it is generally difficult for them "to keep their activities bounded by the realm of *fantasy*." Such persons may come from the "best" homes. They often are well educated and may have high intellectual endowments. Some of the most stirring romantic novels and love poems are written by women of this type. Perhaps from the impress of early training, some turn to religious asceticism.

I should like to quote excerpts from a long correspondence of one woman whom I studied personally over a considerable period of time. She is a brilliant woman whose first marriage was to a quiet, home-loving man who became unbearable to her. She was, in her own words, "boiling over with unsatisfied desires. . . . I have the capacity for murder. I have attempted murder. It seemed very simple to me at the time. I would kill him, for as far as I was concerned there was only one problem to be solved. I don't remember having any plan as to how I would kill him, but since nothing was at hand, and since I looked about for nothing, I suppose I must have intended to strangle him. . . . I should like very much to be the mistress of some man, for a time at least. I like men. I like sexual relations; I imagine I am a little oversexed, although I have no idea just where the 'over' begins.

"The horrible and disgusting thing about this characteristic of mine is that I would not stumble into such a relationship blindly, out of love and passion alone. . . . I would walk into it, urged on by curiosity, lust and an insane pride in my ability to gratify any man without running the risk of extending myself beyond limits. I think I could enjoy sexual relations with almost any intelligent, clean, likable man. The only personal problems of which I can think obtain to religion.

"Something like being in love, *that* is my religion, or my feeling about religion. . . . I do not subject my religion to any critical analysis. Sex must be a great problem to me. I think and write about it so much.

"I do not love any member of my family. I feel pity for my mother and, I suppose, for my father too. My brothers and sisters mean almost nothing to me. If all of them were to die at once I am sure I would not miss them; in fact, I think I would be quite happy to be completely free of their tenaciousness and my responsibilities for them. I wonder if my mother ever guessed the train of thought that tore through my mind when she wouldn't discuss with me (I was then seven or eight) how it felt to sleep with a man."

In another communication she comes back to her religion. "I left quite early . . . and went to St. Mark's. The cold dampness on the way up, followed by the beauty and quiet of the cathedral washed most of it out of my system. At first I felt out of place and almost dramatic kneeling before the Christ statue and praying. It was the first time in months I had knelt and prayed in words. Almost at once that self-consciousness left me. I liked the arches, the tall old dark alters, the statues and the burning candles, and the silence—most of all the silence. I think I can assume a worship-

(Continued on page A-44)

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1. Crumpacker, E. L., et al., AMA Arch. Int. Med., 98:314.
2. Palmer, E. D., "Clinical Gastroenterology" Hoeber-Harper.

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ful attitude in any quiet place, but beauty helps."

From another letter:

"Today I walked with God down a country road,

We talked of common things;

The bend of the tree,

The farmer planting corn.

I forgot that he was God and I only Ina Ann.

I asked, was it funny that I should study plants?

God chuckled and agreed that it was funny that I should study plants.

We made a ship from a cloud.

No one said it was not formed right,

No one cared.

I walked with God."

This woman, while lamenting that she had never had "the thrill" of an orgasmic finale, confessed "unadulterated (*sic*) pleasure" in prolonged coitus. I am convinced, nevertheless, that the conscious failure to achieve an orgasm was a motivational component in her impatient searchings. Her religion, literary tastes, her loves were not simply dominated by sex, they were absorbed in it and were really psychosexual components of it. This woman was not a sex pervert. Though she admittedly had outraged the common law and had felt the urge to murder, she had never been arrested or, to my knowledge, been accused of a crime. She usually exhibited a gentle manner; she had a genuine affection for little children and could love a man anywhere if and so long as she could "love" him in bed. She married at least three different men. All are living. Throughout her restless years she has kept a constant, passionate and unwearying vigil over her children. She has surely suffered more than the normal woman's lot of loneliness. Once in conversation she confessed a recurrent sense of melancholy because of the restive hungers which had lured her from her first marital home.

What strange somber or cruel escapes this personality might have sought if chained for long under the forbearant restraints of an aging and flabby patriarch would be a vain and foolish fancy. I found one such type, a woman who confessed kindred cravings, serving a life sentence for murder in a reformatory for women.

There is a level of conflict where the Cyprian hunger cannot be sublimated. It must find a gratifier or be lured to some wierd form of aberrant behavior which may fall into any one of several psychoneurotic manifestations such as kleptomania, "check writing" and gambling.

Psychosexual Conversion

A strange and sometimes profoundly disturbing psychosexual conversion may follow a novel moment of sexual excitation. An attractive white girl I visited in jail, serving a sentence for cohabitation with a married Negro man, insisted that she would never love a white man. She "never wanted sexual intercourse with a white man again." She said, "When I get out of jail I am going to a large city where I can find and, I hope, marry, a lovable Negro." Investigation revealed that this girl from adolescence had been exploited sexually by white men. She had traded sex for clothes, meals and a place to sleep. Until she met this Negro, she had never experienced sex as a love offering.

One woman, a farmer's wife, and the mother of four children, insisted that prior to one untaming experience sex had never had any significance for her except the satisfaction of a man and the reproduction of the race. On the way home from her father's funeral in a distant state she fell into the company of a strange man, and an unusual circumstance was the provocation for one night together in a hotel. This woman was never a *good* wife after that, however much she admittedly tried to be. She became restless, uneasy and resentful of her husband's approaches. She tried to bury her longings in church work but found herself on the move in response to the most immature excuses. There were very likely secret longings before, but if conscious they were retained behind an exterior of wifely conventionality. Another woman, the wife of a professional man, at 44 slept with a sojourner on a steamer. She returned home a changed and impatient woman. She became indifferent to her housework and to her hus-

(Continued on page A-46)

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band. She spent nameless amounts of money traveling over the United States and other countries always on the pretense of enlarging her cultural vision. She finally was granted a divorce on grounds of incompatibility.

Before turning attention to a consideration of actual sexual perversion let me report a most curious case. I learned about it from a brilliant, cultured widow of one of Washington, D.C.'s most eminent professionals. The subject, who served as a domestic in the home of a close friend of my informant for many years, lost her aged husband after more than a half-century of life together. She was approaching 80 and had reasonably not engaged in actual sexual intercourse for years. The shock of her mate's death apparently set the imagination to playing on the sexual excitations of earlier years. "Everything," as she said, "comes back. . . . I get so hot for him that I must do something." What did she do? Week after week she returned again and again to the mound of earth over her husband's remains. There, with her skirt pulled high, she experienced a real old-time sexual intoxication with all the earlier pleasurable responses. As a climactic manumission, almost without exception, she urinated on the grave mound. My informant assured me that the benevolent mistress had personally driven this trusted servant to the cemetery on several nocturnal occasions for this orgiastic ritual.

Serious students of the anomalies of humankind in the sex realm are aware of the strange effects that an overwhelming traumatic experience may have on the sexuality of an individual. I have reported elsewhere the cases of young men who abruptly turned to homosexual practices following such psychic upsets. I am convinced also that while women are far less likely to turn to dangerous perversions than are men, those who have shared the real pleasurable excitations of sex harbor far more fertile imaginative capacity in the sex domain than do males.

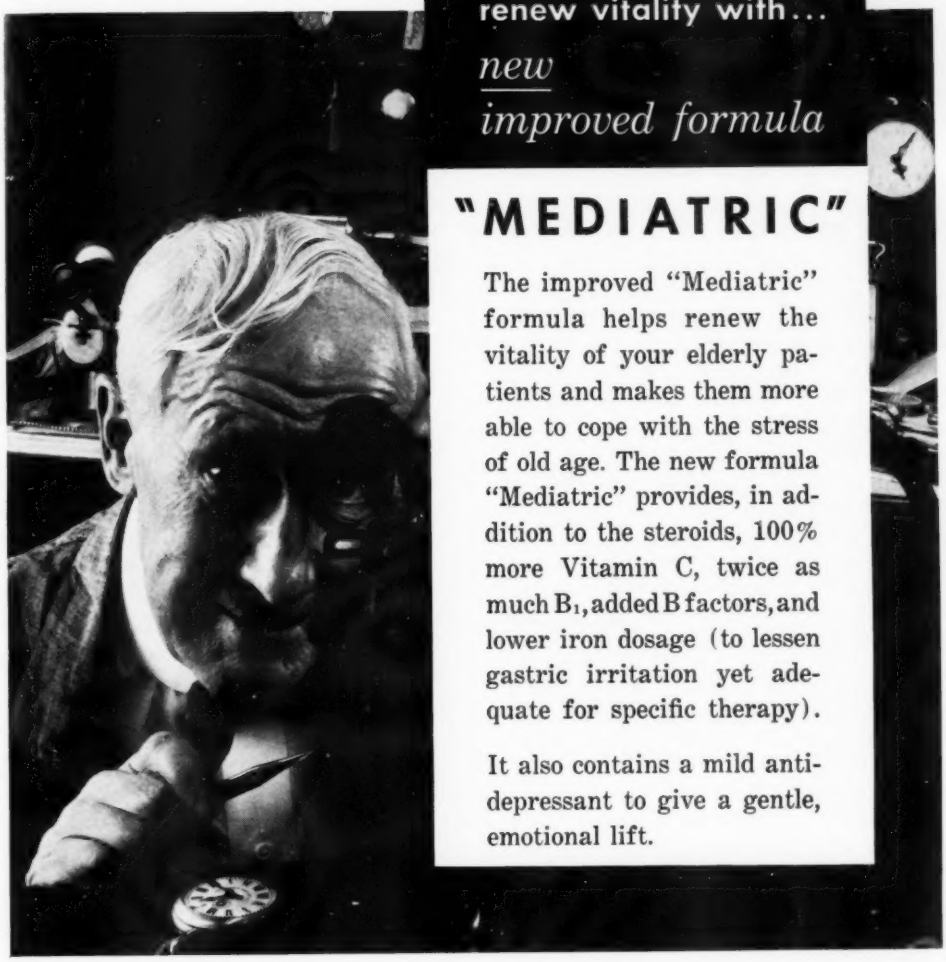
I have here discussed sexual anomalies that exhibit certain unique characteristics of the sort often found in sexual perverts guilty of sexual or other criminal offenses. These individuals, however, are not perverts in my definition of the term. They seek sexual gratification in an acceptably normal sex object. In spite of a variety of unidealized preparatory engagements and substitutions, culmination, where possible, is of the normal manner. In the instances of the strange grave ritual real sexual delights stirred the imagination.

Transvestism

An unusual case of transvestism illustrates how far removed an extravagant sexual deviation may be from a true sexual perversion, and yet, because of culturally conditioned anxieties, provoke criminality. The subject, K., lost his mother when he was four years old. His father remarried two years later. After the birth of her own first child, the stepmother resented and exploited K. and wanted him removed from the house. The father put up no defense for the boy. As a neighbor said, "It was easier that way." When he was about 10 years old, K. was handed over to a maternal aunt. He was 19 years of age and living with the aunt when I came into the case.

K. said that his aunt had been "nicer" to him than anyone else. Although K.'s mentality was subnormal, it was not below the level of normal response to the ordinary life in the small town in which he lived. He lived without plan, but he had a good work record. He thought his employer, an operator of a small produce house, a "nice man." From his earliest memory, he had built dreams about his mother and wondered how she had looked. He kept a fanciful picture of her in his head "all the time." He thought, "If she had lived (he) would not have caused so much trouble." At about eight years of age, he found an old dress that his mother had worn, and he put it on. He said it gave him a feeling of comfort such as he had never had before. He felt as though his real mother were there with him, that she had her arms about him, and that he could talk to her. He hid the dress away and put it on again and again. Sometimes, he would go to bed with the dress on and always "slept better that way." At other times, when he was "lonely or sad at work," he said he found it difficult to continue his work. He

(Continued on page A-50)



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wanted "closing time to come so he could put the dress on."

While wearing the dress, he had a feeling of sexual delight, and later there were occasional episodes of masturbation but "not often." He wished that he could wear a dress to work. He said that he noticed that girls were always treated better than boys. They were "petted." The men who came into the restaurant "talked nice to them." He insisted that this desire to be "talked nice to" was important in his wish to wear a dress. He was not conscious of a wish to have men admire him as a woman. He said that when he wore a dress, people were "nice to him" and that was "all he wanted from them." Like other transvestites he felt out of place in male attire. He said, "I feel lonesome, as if nobody wanted me."

He exhibited almost no interest in sex. He had never had a sexual relationship with a woman and thought he would not want a man to put an arm around him when he was wearing a dress.

This is a unique case of a transvestite development stemming from a mother fantasy. The mother-identification fantasy was not enough to shield K. from the real rebuffs, taunts and exploitations of his environment. He showed no ill will toward his father, or even toward his stepmother. His manner was gentle and he had no wish to injure anyone. His impatience with male attire could be related to a bleak childhood in which he sought shelter in the fantasy arms of a deceased mother, and in an emergent consciousness that the role of even a homely girl was preferable to that in which the male habit had cast him. The onerous burden expressed by all other transvestites I have known was that although they were endowed with delicate feminine natures, they must assume a masculine habitus throughout life.

K. had been arrested several times for dressing like a woman, and once he had been arrested for burglary. He had no explanation for the burglary except that he "didn't know what to do with (himself). . . ." He had "wanted to drive to the city where (he) could get a hotel room and wear women's clothes," but it was late when he quit work. Besides he was broke. He didn't need the things he stole.

True Sexual Perversion

From my point of view, the true sexual pervert is one whose erotic responses require a substitution for the normal sex object stimulus. This does not mean that the normal sex object may not be used, but, rather, it means that its use, if at all, is incidental to the sexual excitation. A sadist who detours the road to danger by killing a chicken in a house of prostitution preparatory to intercourse with a prostitute is a pervert. The woman is incidental to the desire; she serves as an energy-release agent.

Pedophiles are rarely true perverts. Such individuals are generally senile or they resort to children usually because of prolonged failure to deal adequately with adults. In the few cases I have investigated in detail, all but one in prison, there was no evidence of incapacity for sexual stimulation by an attractive woman. Indeed one child rapist confessed that he "had been stirred up by a sexy-looking woman."

Bestiality is, in all cases to my knowledge, a substitute for something more desirable by one who, for inhibitory or other reasons, is denied a normal object. Perversion is defined not in the character of the act but in the psychosexual detachment from the class of normal love objects.

I agree with Franz Alexander that the extremely inhibited or sexually stranded individual in our society, with its polymorphic demands and varying response limitations, may find himself unable to function successfully on a *sublimative* level. Here the strain of conflict may impel to the necessity of finding another and perhaps obscure outlet. The creative quality of sublimated activity is thus sacrificed and the unhappy individual becomes a prey to "forces of disintegration." Threatened from within and without, he neglects those things that one must have to retain an acceptable place in the social order. He slips away from the world of practical reality and loses interest in constructive community enterprises. His *fantasies* tend to become more and more absorbing and morbid. If his perversion arouses suspicion, life from the inside

(Continued on page A-52)

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References: 1. Spies, T. D., et al.: J.A.M.A. 159:645, 1955. 2. Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. 3. Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. 4. Guerra, F.: Fed. Proc. 12:326, 1953. 5. Busse, E. A.: Clin. Med. 2:1105, 1955. 6. Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

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out becomes more difficult to order. Disharmony with the world may drive him into crime-conditioning situations or he may be impelled by his own cruel cravings.

The necrophile, fortunately rare, may steal his victims. The fetishist steals or clips the fetish object. The peeper peeps; the exhibitionist exhibits. Ordinarily that is about all, but not always. The necrophile may murder to obtain an object. Any of these perversions may have more serious components, or any one of these milder perversions may be a component of a more dangerous one such as sadism or lust murder.

Examination of letters written by homosexuals to each other reveals a rise and decline of destructive tensions with the changing fortunes of the hour. In practically all cases a sense of security is tenuous. Once an *affaire d'amour* is shattered, the individual's preoccupation with memories of transient moments, torturing loneliness and anxieties may turn him to fruitless searches, joblessness and sometimes crime.

Sadistic cruelties are not coordinated with any other aims than the satisfaction of the compulsive demand. Such perverts have no wholesome or utilitarian outlet for excess excitation or for the re-establishment of equilibrium. The crimes that sadists commit are of a different motivational order from those of the homosexual. The homosexual's eroticisms run the entire scale familiar to the heterosexual, but for a different class of objects. There is for the homosexual no acceptable sexual substitute and generally no accessible level of sublimation. The homosexual can wonder how it would seem to be normal sexually, but generally he cannot desire normal sexuality. His imagination is bounded by the sexual cravings that he knows. The urgencies of his closed world, the hazards of approaching strangers in the adult male population, the scanty supply of suitable sexual objects, and his relatively unprotected amatory status may encourage robbery or blackmail of his own kind or an irresistible interest in young boys.

The investigator comes upon a variety of harmless and sometimes ludicrous sexualizing associations. Dr. David Abrahamsen has reported the case of a woman who had become conditioned to bidding off the nuptial bed. Without this bidding the sex act had little pleasurable significance. The bids went higher until the orgasm was achieved. It is significant that the bids had to be real, not fantastic. I reported elsewhere the cases of two women who had become conditioned to mild masochistic necessities in the sex act. Both stated that orgasm was impossible until the husband "cussed," used "foul language" or simulated sadistic cruelty. He could not, however, get too far out of the bounds of reality. One, for example, made the mistake of calling his wife a "goddamn whore." The word "whore" brought the response system to a halt.

Such harmless "bed" comedy has only incidental interest for the criminologist. Yet it would be a mistake to assume that the inoffensiveness of such behavior is in some unique quality of the conditioning process. The harmlessness is in the fact that the behavior is mutually shared and mutually confined and, though abnormal and compelling, it heightens a mutually legitimate pleasure and brings the couple to a desirable erotic consummation.

Where gratification is not obtainable legitimately and there is no substitute, a retreat from reality and sometimes to criminality may be the only outlet. Under the stress of criminal necessity the "obligation principle" is fragmented. It becomes unserviceable and finally vanishes. In the process of disintegration the individual may be caught in other "escape" traps such as alcoholism and drug addiction. The alcohol or drug comes first as a release but eventually breaks down the personality *staying* forces. The element of inner conflict is liquidated by irresistible tensions. The perversion thus gains an advantage by destroying the inner moral censure. Without effective opposition the compulsive forces are not restrained. The process reminds one of the overindulged boy who drugs his father into a state of nonresistance to claims on his exchequer only to find eventually that the father has been drugged out of his earning powers. Such tension-escapes always destroy the constructive forces, never the destructive ones.

(Continued on page A-54)

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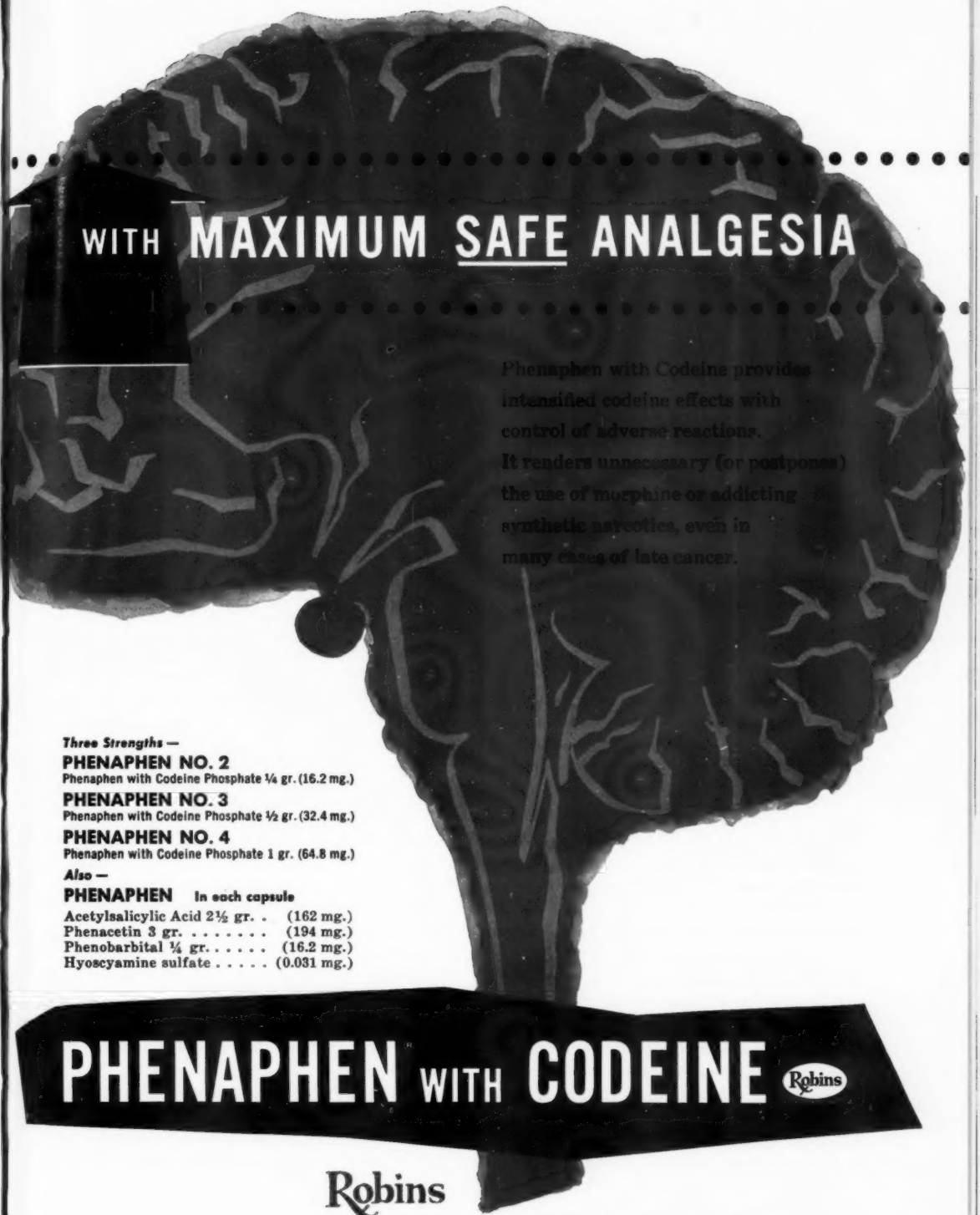

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In some cases of great sensitivity the organism remains in a more or less perpetual state of excitement for prolonged periods. Normal controls apparently have never had a chance to be deeply channelized. Such appears to have been the case with the artist who murdered four persons within hardly more than an hour. The murders were all committed in the house where the artist had gone to kill an attractive young model whose very presence had kept him sexually excited over a considerable period of time. The artist later confessed his inability to endure or control the tensions that the very thought of this girl created in him. On the surface he had, to my knowledge, aroused no murderous suspicions.

Unchanneled sexuality may break out in almost any very exciting situation. In the absence of competing controls the insatiable excitation may set up the necessity to destroy the object of desire. Men of this type are perhaps the most difficult of all to predict, for they often exhibit a warm sensitivity to the ennobling arts. Such a one spends much of his time living miserably, for his sensitive nature is unanchored to any durable system of meaning.

Pyromania

One of the most dangerous kinds of perversion and one of the most responsive to therapy in its early stages is sex pyromania. On the basis of my own observations I believe that pyromania begins with a very sensitive and insecure organism in an abnormally prolonged state of tension. As noted, an unhappy sensitive individual under prolonged tension may experience a sexual pleasure in almost any condition of great excitement. The first experience may come about quite accidentally. In time the recurring desire for repetition of the experience takes over the wish and the will. Robert Dale Segree set his first fire when about eight years of age. With increasing age the sexual satisfaction, and hence the desire to set more fires, grew in intensity until all consideration of consequences disappeared. No one knows how many fires Segree set, or the damage to life and property that they caused. At 20 he burned down the Ringling Brothers-Barnum and Bailey Circus tent in Massachusetts and the fire killed 169 persons in six minutes. He had been arrested previously for setting fire to a navy pier, a schoolhouse and a Salvation Army building. After the circus fire he confessed that he had been haunted for years by strange "fiery dreams," phantom scenes and "flaming red riders on fiery horses."

Murder

There is not space here to discuss the complex motivational content in the cases of such chain murderers as Landru, Watson, Fish and, more recently, Gein in Wisconsin. I am convinced that there is a delusional aspect in practically all such cases, although there is a wide difference in the quality and sources of the delusion. Certainly Landru and Watson were driven by a complex of motives, one of which, though variable, was money. Money was not, however, a constant impellent; they sometimes sought women known to have no money. The ego not only feeds on the arts and tricks and success of the pursuit and the possession, but by its nature, once having completely conquered, cannot leave the victim for another; nor can it bear to be troubled by an old victim in future exploits. The motivational content varies. Certainly a Watson or a Landru is impelled by a different complex of forces from that of a Fish or a Gein. Fish and, I believe, Gein (although I have not had a chance to study his case), were driven by singular delusions arising out of inner conflicts due primarily to a basic personality defect, an inadequacy to satisfy an absorbing demand of the organism through normal channels. Such a state of inhibited craving in a fundamental realm of the individual's nature finds refuge in strange fantasies that become more grotesque and morbid until the psychosexual fantasies totally obsess the personality. Such an individual must know what the object is like, must explore it to its depths; he must identify with it, possess it utterly and without a challenge to his morbid curiosity. He must examine it and sometimes taste it, at least the parts on which his fantasies have played.

It is hard for the ordinary person conditioned to the sexual ways of ordinary men to

grasp the nature of a sadistic murderer. The problem is even more difficult if the murderer has committed no known previous offense. All such murderers are alike in one respect: They have lived many years in a world of cruel and grotesque *fantasy*. If we could actually see the strange and brutal fantasies on which the imagination of such a criminal has played for years, the behavior would not be so difficult to understand. A difficulty of investigating such types is the fact that the motivational content behind the crime has been built up over a period of years beneath a gentle appearance and often a pietistic timidity.

Such murderers have often felt quite secure in this little world of brutal fantasy. Like a narcotic drug, however, the absorbing fantasies become more morbid and cruel. Finally the compelling desire can no longer be contained within the realm of fantasy. In spite of a certain commonplace appearance, the inside has lost rapport with the world of reality. Investigation reveals that such individuals often tend more and more to avoid normal social engagements. They may find increasingly frequent excuses for avoiding the company of other people of their own age or social status. What is more, they tend to show a decreasing interest in the broader aspect of community welfare, though not unusually such a person may be profoundly religious. Social position, occupation, intelligence and formal education may offer little in the way of workable clues to identification. Over and again, such pathologic degenerates are so well shielded beneath a commonplace exterior as to make it extremely difficult for the investigator to bring himself to the task of seeking out the unusual and abnormal in the secreted life of the individual.

ACKNOWLEDGMENT

I am indebted to the Nebraska Police Officers' Association and its Board of Directors for financial assistance for research in the field of sex anomalies and offenses.

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1. Reinhardt, J. M.: Sex Perversions and Sex Crimes. Springfield, Illinois, Charles C Thomas, 1957, p. 6.
2. *Ibid.*, p. 5.

MEETINGS and Postgraduate Courses

Academy of Psychosomatic Medicine, New York: Fifth annual meeting, October 9-11, at the Park Sheraton Hotel. For further information, write to: Dr. Bertram B. Moss, Suite 1035, 55 East Washington Street, Chicago 2.

American Heart Association, San Francisco: Thirty-first annual scientific session, October 24-26, at the Civic Center. For further information, write to: Dr. F. J. Lewy, Assistant Medical Director, American Heart Association, 44 East 23rd Street, New York 10.

Gerontological Society, Inc., Philadelphia: Eleventh annual meeting, November 6-8, at the Bellevue Stratford Hotel. For further information, write to: Dr. Warren Andrew, Bowman Gray School of Medicine, Winston-Salem, North Carolina.

International Congress of Gynecologists and Obstetricians, Brussels: To be held on July 18-19. For further information, write to: Dr. G. Geeraert, 311 Avenue Louise, Brussels, Belgium.

Inter-Society Cytology Council, New York: Annual scientific meeting, November 13-15 at the Hotel Statler. For further information, write to: Dr. Paul F. Fletcher, Secretary, 634 North Grand Avenue, St. Louis 3.

New York University Post-Graduate Medical School, New York: Postgraduate course on the physiologic basis of clinical electrocardiography, June 2-6. For further information, write to: The Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

University of Colorado Medical Center, Denver: Postgraduate courses for 1958:

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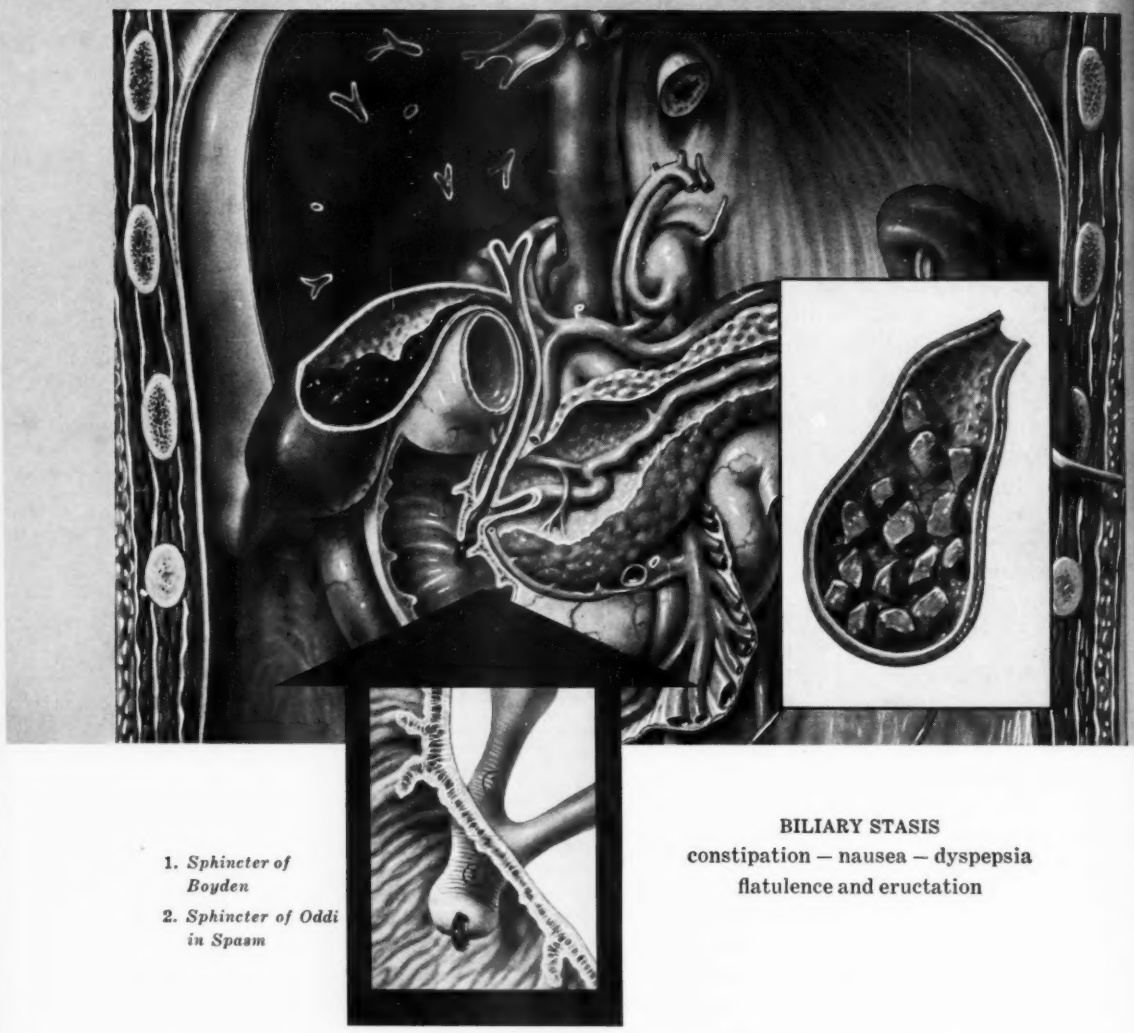
Dermatology for general practitioners, July 10-12
Ophthalmology, July 21-24
Seventh Annual Western Cardiac Conference, August 11-16
The prevention and management of athletic injuries for team physicians, coaches and trainers, August 25-27
Pediatrics, September 4-9

For further information, write to: The Office of Postgraduate Medical Education, The University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20.



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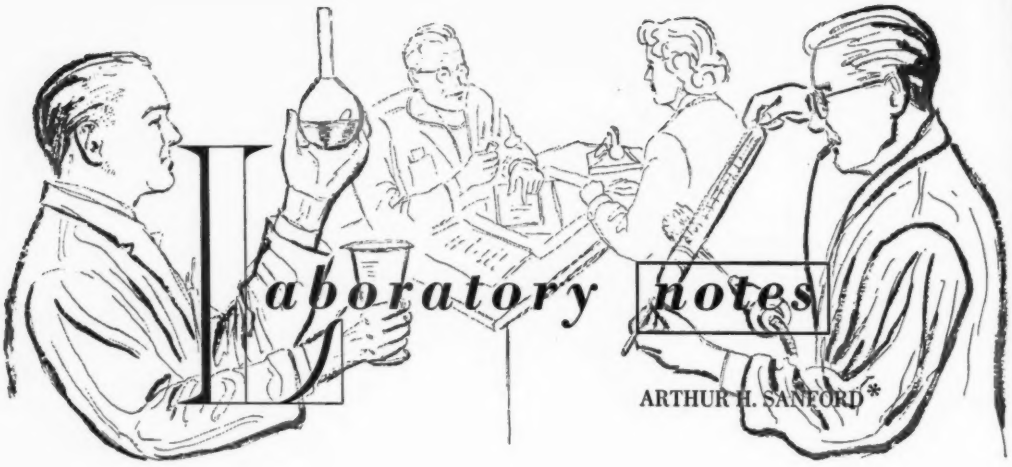

ARTHUR H. SANFORD*

Phenylketonuria

You will realize immediately that this column is to be about phenylpyruvic oligophrenia—and how impressive these euphonic Greek syllables sound from the mouths of neuropsychiatrists!

Dorland's dictionary defines phenylketonuria as "a congenital faulty metabolism of phenylalanine, because of which phenylpyruvic acid appears in the urine. It is often associated with mental defects (phenylpyruvic oligophrenia)."

Oligophrenia means "little mind," or "feeblemindedness." It has been known for more than 20 years that phenylketonuria occurs in some persons so afflicted. In 1938, Jervis[1] reported that the amount of phenylpyruvic acid excreted by a mentally defective patient increased when he was fed phenylalanine. These clean-cut feeding experiments, in which accurate quantitative methods were used, led to the conclusion that there was an inhibition in the metabolism of phenylalanine (phenylaminopropionic acid) at the stage of phenylpyruvic acid, and that the patient was unable to oxidize this keto acid at a normal rate.

It has also been demonstrated that there is a very simple qualitative test for phenylpyruvic acid in the urine. Acidify a sample of urine with a few drops of dilute sulfuric acid and then add a few drops of 5 per cent ferric chloride. This is essentially the same reagent used in the test for chlorpromazine.[2] A positive test shows a dark green color.

Several years ago, the late Dr. D. E. McBroom made a survey of 1,024 patients at Cambridge, Minnesota. Urine from 805 epileptic patients gave negative findings in all cases; urine from 4 of 219 nonepileptic, feebleminded patients showed the characteristic green reaction.

The reason for calling your attention to this interesting finding is a recent letter to the *Journal of the American Medical Association* from Dr. Williard R. Centerwall,[3] College of Medical Evangelists School of Medicine, Los Angeles. He describes a "simple diaper test" (and I was tempted to use this as a title for this column).

The Los Angeles City, the Los Angeles County and the San Bernardino County health departments are cooperating with Dr. Centerwall's group in tests at well-baby clinics. The test consists of putting a drop of 10 per cent ferric chloride solution on a freshly wet diaper. The characteristic blue-green color will appear at

(Continued on page A-70)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

Documentary Case History . . .

Hypertension controlled for four years with Serpasil®

(reserpine CIBA)

K. C., a 67-year-old retired shirt manufacturer, had a 16-year history of hypertension, was troubled by recurrent dizzy spells and headaches. "I'd get several attacks a day. . . . Usually I'd go into the bedroom and lie down." Serpasil therapy was started four years ago, effecting a gradual reduction of the patient's initial blood pressure of 220/120 mm. to the present 140/80. Now well and asymptomatic, ". . . I'm able to go to matinees and see some of the TV shows."

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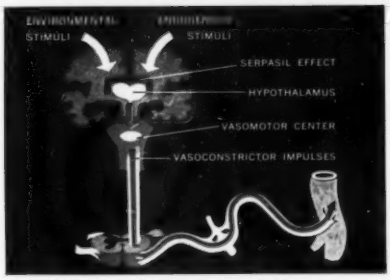

Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

C I B A SUMMIT, N. J. 2/2585MR

once in a positive reaction. Apparently, a few infants, about four weeks of age and older, may show this substance in their urine. Positive reactions may be verified by the more accurate 2,4-dinitrophenylhydrazine test.

This group of workers believes that a phenylalanine-restricted diet, if started early enough, may prevent mental deficiency. It is possible that this special diet may not be necessary after the child is two or three years old. Dr. Centerwall[4] also reports that similar studies are being carried on in England.

It seems to me that every reader of this column who sees a four week old infant can perform this simple diaper test. If, by so doing, one such infant may be saved from becoming mentally defective, the effort will not have been in vain.

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2. Sanford, A. H.: Test for chlorpromazine in urine. Postgrad. Med. 22:A-58 (July) 1957.
3. Centerwall, W. R.: Correspondence on phenylketonuria. J.A.M.A. 165:392 (September 28) 1957.
4. *Ibid.*, p. 2219 (December 28) 1957.

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REFERENCES—(1) Settel, E.: Personal communication. (2) Holley, H. L.: Personal communication. (3) Burns, J. J.; Trousof, N., and Brodie, B. B.: To be published. (4) Smith, R. T.: To be published. (5) Peak, W. P., and Smith, R. T.: To be published. (6) Wiesel, L. L.: Personal communication. (7) Passarelli, W. W.: Personal communication.

CLINICAL RESULTS WITH PARAFLEX

Investigator	Disorder	Number of patients treated	Number of patients benefited	Comment
Settel[1]	acute low back pain, acute traumatic myofascitis, or osteoarthritis	15	14	response excellent in nine, good in five
Holley[2]	wry neck, cervical spondylitis, and disc syndrome	10	10	improvement, ranging from some amelioration of symptoms to profound relief
Wiesel[6]	advanced osteoarthritis	12	10	less muscle spasm and pain
Passarelli[7]	degenerative and rheumatoid arthritis	9	9	improvement, with less stiffness and freer motion
Passarelli[7]	varied arthritic rheumatic, and traumatic disorders	6	6	less stiffness, less pain
Totals		52	49	

*Trade-mark †U. S. Patent Pending

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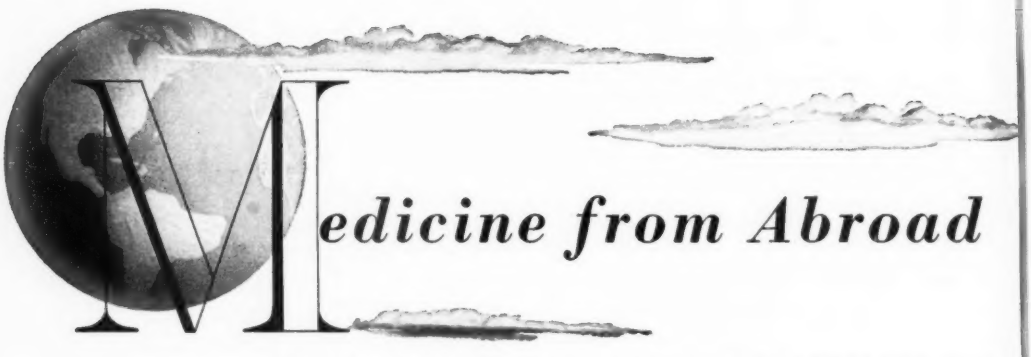


Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Genital and anal conditions in children—In a recent issue of the *Australian Medical Journal*, staff members of the Royal Children's Hospital, Melbourne, discussed problems associated with diagnosis and treatment of various testicular, vaginal and anal conditions in children.

Dr. Peter Jones ("The superficial inguinal pouch and the undescended testis") found that a normal retractable testis is distinguishable from a superficial inguinal ectopic testis in the pouch. When the testis is normal, there is free communication between the pouch and the scrotum which is absent in the latter condition due to abnormal attachments of Scarpa's fascia to the pubic tubercle.

Drs. Sloman and Mylius ("Testicular infarction in infancy; its association with irreducible inguinal hernia") pointed out that irreducible hernias caused one-third of all testicular infarction found in children admitted to the Royal Children's Hospital from 1951 through 1954. The remaining cases were due to torsion of the testis. They also found that testicular infarction due to irreducible hernias occurred almost exclusively in the first three months of life.

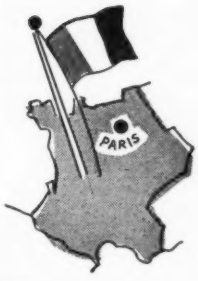
Since the inexpansible coverings of the spermatic cord are considered to be the sites of constriction of the blood supply to both the testis and hernia, they recommend prompt operative repair of inguinal hernias in infants less than three months old. An inflatable truss should be used if the operation must be postponed.

Writing on "Minor surgical conditions of the anus and perineum," Dr. F. Douglas Stephens stated that fissure of the anus in children is very different from that in adults. In children, the fissure is a mucosal split which heals very quickly and is caused by large-caliber stools. Treatment should be directed not to the fissure, but to the underlying condition of constipation.

Idiopathic rectal prolapse, a condition common in young children, generally is self-limited in its duration. Conservative measures usually terminate the tendency to prolapse, and only rarely are operative procedures required. In a further discussion of abnormal anal conditions, Dr. Stephens reviewed the problems associated with rectal polyps, postanal dimple and hemorrhoids. This report also stated that adherent labia minora create more problems by being wrongly diagnosed as congenital absence of the vagina than by being treated, since treatment is simple and effective. Vaginal discharge in small girls is also discussed, particularly in regard to its etiology and treatment.

(Continued on page A-79)

FRANCE



New methods of reducing high blood cholesterol levels—In his study of agents which modify the serum lipids, published in *La Presse médicale*, De Gennes elected to determine first the action of heparin on the lipids.

He found that heparin and its derivatives will lower the electrophotometer-measured optic density by a wavelength of 6500 A. (heparin clearing factor). The concentration of the lipids and cholesterol and the values found in the Kunkel test are reduced. Determined according to Williams' clearance constant, the clearance can be drawn by a hyperbolic curve. The mode of action of heparin is indirect; it occurs within the plasma and is focused on the hydrolysis of the triglycerides.

Although heparin produced an undeniably therapeutic effect in patients with a high level of blood cholesterol, it was inconstant and insufficient. The serum values indicated that the effect lasted only a very short time.

De Gennes also studied the action of protamine sulfate. This substance seems to be a poor choice of treatment, since its action is that of an antihistaminic agent. When mixed with protamine, the serum will first become opaque and then will clear. Electrophotometric findings show that the initially doubled or tripled values of opacity will immediately drop. The optic density follows a hyperbolic curve which reaches a point much lower than the initial value. This curve is in no way related to the initial value of serum lipids. The greatest reduction rate of the lipids is at 37° C. The reducing action is destroyed by heating the serum to 50° C.; it is also destroyed by adding a mixture of protamine and heparin.

Numerous experiments with protamine on animals and humans showed a nearly constant and rather long-lasting effect. In humans, the author proceeded with slow perfusions of 10 ml. of a 1 per cent solution of protamine sulfate, which he repeated daily. In normal subjects, the clearance began after a few minutes. It reached its maximal value in four hours and continued for 24 hours. In optic opacity, blood cholesterol and lipid levels and in the values of the Kunkel test, the drop amounted to about 25 per cent.

De Gennes did not attempt to treat patients who had a large-scale renal insufficiency, an allergy or far-advanced forms of atheromatosis in which an imminent cardiac infarction was possible. The results in the atheromatous patients were comparable to those obtained in normal subjects. The outcome was spectacular in cases of essentially high levels of the blood lipids and in cases of xanthomatosis with high blood cholesterol levels. Mediocre effects of rather short duration were obtained in patients with lipoid nephrosis or with amyloid degeneration of the kidneys or myxedema, or both. There was no success in cases of infectious jaundice. In hepatic patients with a high level of blood cholesterol, a reverse effect, with opacification of the serum, was observed during this therapy.

Supplemental experiments were performed on chickens and rabbits in which a high level of blood cholesterol had been experimentally provoked by giving them a diet overloaded with lipids. In these animals the components of lipid metabolism were lowered by about one-third.

Following the investigations of De Gennes, Laudat tried to develop a simpler, more manageable medication derived from the protamines. His medicament combines such agents as propionic, hydroxypropionic, isovaleric, methylvaleric and acetic acids. The preparation was experimentally tried by Ruffie, who then used it in therapy. His method of treatment consisted of muscular injections of 5 ml. of a 2 per cent solution of the preparation. He gave several patients two or three series of five injections each at 15 day intervals. After one or two series, which consumed about a month's time, Ruffie found that the treatment had an apparently lasting effect in the majority of cases of hypercholesteremia.

In these studies, there were 82 patients who had an abnormally high blood cholesterol level. This condition was accidentally detected in the course of general physical examinations; the patients were without any clinical manifestations of atheromatosis. In 31 patients it was proved that atheromatosis was present. Though not sufficient in number to have a statistical significance, there were also some cases of essential hypercholesteremia, diabetes and lipoid nephrosis. The treatment had no untoward effect.

Although they are extremely cautious in their conclusions, the authors believe that the procedures just described will prove to be effective in treating high blood cholesterol levels and in preventing atheromatous degeneration.

(Continued on page A-82)

Fats contain a wide variety of fatty acids. Certain of these fatty acids are called "essential" . . . essential to the body for functioning in some vital and specific role . . . essential in foods because the body cannot synthesize them.

These "essential" fatty acids are called arachidonic and linoleic. Arachidonic acid is found only in animal fats . . . and is believed to be the functional fatty acid specifically required in cell metabolism. Linoleic and a related acid, linolenic, are found in vegetable oils. Linoleic acid is readily converted to arachidonic acid in the body. All these acids are easily destroyed by oxidation or hydrogenation.

Different fats contain different amounts of "essential" fatty acid. While unprocessed vegetable oils contain larger quantities than do animal fats—when hydrogenated, their "essential" fatty acid content may be similar to that found in animal fats.

In the body, "essential" fatty acids are found in vital organs such as kidney, heart and liver. They have been shown to be dietary essentials for many species of animals . . . and recent evidence from studies with infants suggests they may be dietary essentials for man as well. Animals fed diets deficient in "essential" fatty acids cease to grow . . . lose hair . . . develop dry and scaly skin which is permeable to water . . . show kidney damage . . . become sterile . . . and die prematurely. There is indication that "essential" fatty acids are involved with cholesterol metabolism . . . or transport for an "essential" fatty acid deficiency develops more rapidly in experimental animals when the metabolism of cholesterol is increased . . . by feeding excess cholesterol . . . or by making the animal diabetic or hypothyroid.

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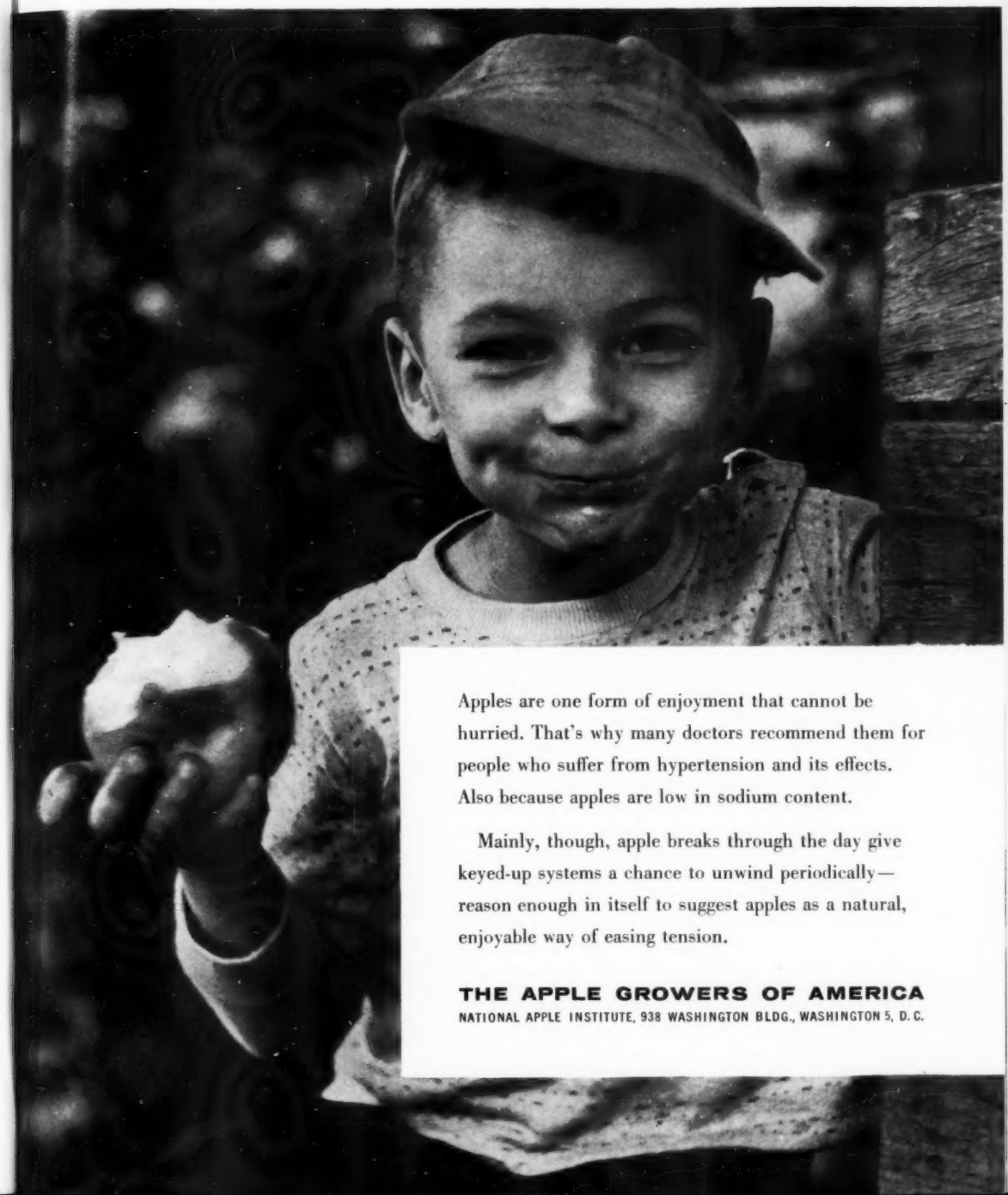

Apples are one form of enjoyment that cannot be hurried. That's why many doctors recommend them for people who suffer from hypertension and its effects. Also because apples are low in sodium content.

Mainly, though, apple breaks through the day give keyed-up systems a chance to unwind periodically—reason enough in itself to suggest apples as a natural, enjoyable way of easing tension.

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ENGLAND

Disturbances of renal physiology—At a recent discussion on this subject at the Royal Society of Medicine, Dr. A. A. G. Lewis pointed out that the kidneys are partly responsible for maintaining the volume and composition of the body fluids within narrow limits, and that they may fail in this task, even when perfectly healthy, if disturbances elsewhere in the body bring about changes in their function. Extrarenal influences which may disturb renal function are: (1) reduced renal blood flow; (2) abnormal humoral or nervous influences; (3) urinary obstruction; (4) when the kidney, in carrying out one task, is prevented from performing another. The renal blood flow and glomerular filtration rate are reduced when the cardiac output falls after hemorrhage. They are reduced by preoperative medication with morphine or PETHIDINE® and by anesthesia, while fairly severe hemorrhage, operative procedures, or the reduction of blood pressure by ganglion-blocking agents produces little further fall. Moderate falls in glomerular filtration do not have much effect on the composition of the urine. Falls in the glomerular rate are produced by hypothermia, and it is significant that these are unaffected by the administration of high spinal anesthesia.

One situation is particularly important—after a major operation the urine volume is found to be greatly reduced. Pre-existing dehydration or blood loss may have been severe and not fully corrected, so that the urine is highly concentrated with high specific gravity and urea and low sodium, indicating good glomerular and tubular function. A similar urine may be passed as a result of the usual endocrine response to surgery, and only clinical examination may differentiate this from the first situation; or severe blood loss and shock at the operation, perhaps temporarily masked by anesthesia but becoming apparent later, may have led to urinary suppression from reduction in renal blood flow and glomerular filtration rate. If this has been allowed to persist for very long, acute tubular necrosis may have occurred, since the urine volume is very low, the specific gravity is little raised, and little modification of plasma concentration of the solutes has occurred. The blood urea therefore rises rapidly, and, for practical purposes, the kidney now has no excretory or regulatory function.

The changing etiology of erythema nodosum in children—During a meeting of the pediatrics section of the Royal Society of Medicine, Dr. John Lorber and Dr. T. Colver of Sheffield reported on a consecutive series of 106 children with erythema nodosum seen between January 1951 and December 1956. Sixty-six of the children (62 per cent) were tuberculin-positive as a result of tuberculous infection, five (5 per cent) had had BCG vaccination, and 35 (33 per cent) were tuberculin-negative. These figures contrast with an 88 per cent incidence of tuberculous infection among 100 children, partly from the same unit, reported by Doxiadis in 1949. There was a progressively falling proportion of children with a positive tuberculin reaction. Tuberculin tests were positive in 73 per cent of 49 children with erythema nodosum seen from 1951 to 1953, but in only 53 per cent of 57 children seen from 1954 to 1956. A positive tuberculin reaction is not necessarily an indication that tuberculosis was the only or the main predisposing factor unless there is evidence of recent tuberculin conversion, the presence of an active tuberculous lesion and other possible causes having been excluded. In the whole series, an active primary tuberculous lesion was seen in 46 children (43 per cent). In 10 of these various forms of tuberculous diseases (apart from the erythema nodosum and the primary complex) developed during observation. For this reason, it is suggested that children with active primary tuberculosis associated with erythema nodosum should be given antituberculosis chemotherapy. In 20 children (19 per cent), the only evidence of tuberculosis was a positive skin test.

Treatment of chilblains—A controlled clinical test in general practice has been carried out by the Southeast of Scotland faculty of the new College of General Practitioners, with reference to the effect on chilblains of a new substance, phenoxybenzamine (DIBENZYLINE®), which opposes the vasoconstrictor action of the sympathetic nervous system. Lactose was used as a control; the physicians concerned received equal numbers of bottles of the phenoxybenzamine and the lactose, but the sequence of each set differed. The action of the drug was explained to each physician taking part, and the possible

(Continued on page A-84)

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undesirable effects were described. The patients were told that they were taking part in the trial of a new drug, and treatment was begun cautiously with 1 capsule every day, which was increased up to 3 capsules a day if no undesirable effects had occurred. A series of 128 patients was treated, and in 103 cases the results were analyzed, the remainder being rejected for various reasons. The results were significantly better in the patients who received the phenoxybenzamine than in those who received the control substance, and it is therefore concluded that this new drug has a definitely beneficial effect in treating chilblains.

London fog—The Department of Scientific and Industrial Research has in recent winters been carrying out measurements on smog in London. Following this, Mr. Robert E. Waller, B.Sc., and Dr. Patrick J. Lawther of St. Bartholomew's Hospital have published their observations (Brit. M. J. 2:1473, 1957) on the effects of London fog on a group of 180 patients with chronic bronchitis and emphysema living in Greater London. Special reference also was made to the concentration of atmospheric pollution measured in Central London. The patients attended a special clinic at the hospital and were given diaries in which to record daily their own assessment of their health by means of a special code. The daily concentration of smoke was correlated with the degree of illness. Smoke was intended to serve only as an index of atmospheric pollution in general, since the concentrations of sulfur dioxide and most other pollutants follow a similar pattern. Nearly all sharp increases in smoke concentration, which represented sudden increases in pollution, were followed closely by marked increases in the degree of illness. On most occasions when pollution was high, the visibility was low, this being due either to the smoke itself or to accompanying fog. A fairly close correspondence was found between periods of low visibility and peaks in the degree of illness. The association was not, however, as close as with the concentration of smoke itself. There was also a close correlation between the concentration of pollutants in the air and the clinical condition of the chronic bronchitic patients. In general, their condition began to deteriorate as soon as the concentration of smoke rose, and they took several days to recover. Dense wet fog was observed only rarely in Central London, and it did not seem to enhance the effects of high atmospheric pollution.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-138.

Child Care and Training. By Marion L. Faegre, formerly Assistant Professor of Parent Education, John E. Anderson, Professor of Child Development, and Dale B. Harris, Director, Institute of Child Development and Welfare, University of Minnesota, Minneapolis. Ed. 8. 300 pages, illustrated. 1958, University of Minnesota Press, Minneapolis. $3.00.

Practical Electrocardiography. By Henry J. L. Marriott, M.D., Associate Professor of Medicine, University of Maryland, Baltimore. Ed. 2. 226 pages, illustrated. 1957, The Williams & Wilkins Company, Baltimore. $5.00.

Principles of Ophthalmoscopy. By John K. Erbaugh, M.D., Norristown State Hospital, Norristown, Pennsylvania. 69 pages, illustrated. 1957, Charles C Thomas, Springfield, Illinois. $5.50.

Einführung in die Augenheilkunde. By Dr. P. A. Jaensch. 248 pages with 197 illustrations. 1957, Georg Thieme Verlag, Stuttgart, Germany. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York. $6.55.

The Human Ear Canal. American Lecture Series. By Eldon T. Perry, M.D., Instructor in Dermatology, Wayne State University, Detroit. 116 pages with 40 illustrations. 1957, Charles C Thomas, Springfield, Illinois. $4.75.

The Good Housekeeping Book of Baby and Child Care. By L. Emmett Holt, Jr., M.D., Director of Pediatric Service, Bellevue Hospital, and Professor of Pediatrics, New York University College of Medicine, New York. 288 pages, illustrated. 1958, Appleton-Century-Crofts, Inc., New York. $4.95.

How to Write Scientific and Technical Papers. By Sam F. Trelease, Columbia University, New York. 185 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $3.25.

Ulcerative Colitis. By Harry E. Bacon, M.D., Professor and Head, Department of Proctology, Temple University Medical Center, Philadelphia. 395 pages with 184 illustrations. 1958, J. B. Lippincott Company, Philadelphia and Montreal. $15.00.

Tuberculosis; Every Physician's Problem. By J. Arthur Myers, M.D., Professor of Internal Medicine and Public Health, Medical and Graduate Schools, University of Minnesota, Minneapolis. 290 pages with 75 illustrations. 1957, Charles C Thomas, Springfield, Illinois. $7.50.

SPECIAL ISSUE

Postgraduate Medicine

University of Minnesota Medical School

ROBERT B. HOWARD, M.D.

Guest Editor

MAY 1958

Introduction

THE invitation to be responsible for this issue of POSTGRADUATE MEDICINE was timely, for it has provided us with a welcome opportunity to pay tribute to Dr. Harold S. Diehl, Dean of the University of Minnesota Medical School. The authors of all of the articles in this issue were appointed to their academic positions during the period of Dr. Diehl's deanship and are representative of the many fine appointments he has made. Similarly, the articles themselves are representative of the high quality and the diversity of the research that has characterized this period. It is fitting, then, that this issue be dedicated to Dean Diehl.

Last summer he announced his acceptance, effective November 1, 1957, of a new and important position, Senior Vice-President for Research and Medical Affairs, and Deputy Executive Vice-President of the American Cancer Society, a post that will permit him to contribute significantly to American medicine for several years beyond the time, June 1960, when retirement from the University would have been compulsory. During the current academic year he is dividing his time, serving both the Cancer Society and the University.

The unanimous reaction of members of the faculty to the announcement of the Dean's plans was, at first, shocked disbelief, then, genuine regret at the prospect of losing the services of the man who has given our School such outstanding leadership for nearly a quarter of a century. For most of us it has been just about impossible to imagine the Medical School without Dr. Diehl at the helm.

The *Minneapolis Star* noted this development at our institution in an editorial headed "A great dean." We can think of no better description of Dr. Diehl than this simple, meaningful phrase.

Why has he been a great dean? How has he been able to preside so successfully over the fortunes of the Medical School during a period of remarkable development and expansion, a period of momentous changes in medicine, a period in which Minnesota took its place among the nation's finest medical schools?

We are sure Dr. Diehl would be first to admit that a dean's success, like that of a football coach, depends to a very large extent on his "material," the quality of the "players" on his team. But unlike a football coach, a dean, because he is seeking the services of avowed professionals, may recruit actively and openly. Chance does not determine a dean's "material"; rather, he himself bears the final responsibility for selecting his own "players." Dr. Diehl has demonstrated an uncanny ability to select the right people. This ability is evidenced by the frequency with which his advice is sought concerning appointments in other schools.

Having selected outstanding persons as faculty members, Dr. Diehl has perhaps been at his very best in his dealings with them, in "keeping them happy."

Always patient and at least outwardly imperturbable, he gives a careful hearing to any staff member who wishes to state his views. His decisions are reached only after consideration of all available evidence and all viewpoints. Consider, for example, how he deals with requests for funds and facilities from the various departments. These requests are almost always individually reasonable and justifiable, yet usually their total exceeds available resources. This disparity between requests and available funds the Dean has regularly reconciled solely on the basis of what would best serve the over-all objectives of the Medical School. What is more, he has been able to make clear to all faculty members concerned the sound reasons for his decisions. The head of one major department recently described this quality well: "One of Harold Diehl's great strengths," he said, "lies in the fact that he has been neither a 'yes man' nor a 'no man.' He does not promise or appear to promise everything to everybody, nor does he oppose things just as a matter of general principle. His dealings with his faculty have always been open and extremely fair."

His comprehensive understanding of medical education is, of course, to be expected and scarcely requires comment. But what is worthy of special mention is Dr. Diehl's sharp awareness that a most important mark of a good physician is his knowledge of the basic medical sciences together with the ability to apply their principles to his practice. As a result, basic science departments have received his strong support and have thrived during his tenure as dean.

The *sine qua non* of a medical school is, of course, the medical student. A good dean must understand his students, know their needs, motivations, interests. During Dr. Diehl's years of service to the Medical School, students have known him as friend and wise counselor.

A successful dean must also thoroughly understand all aspects of financing his institution; he must know possible sources of funds and be persuasive in marshaling support. Dr. Diehl has proved himself to be without a peer in this aspect of medical school administration.

Still other qualities have contributed to Dr. Diehl's success as a dean, qualities that are less definable than the foregoing. Dignity, warmth, human understanding, a sense of humor, all are attributes which he possesses in rich supply, and without which he could not have been nearly so effective. The Dean's good health and boundless energy and the help of his charming, understanding wife have also been essential. Renowned and respected nationally and internationally, Dean Diehl has caused his influence and that of the Medical School to be felt in widespread areas of the world. For many, many years to come, we are sure, the words "the Dean" will evoke among his host of medical friends only one image—that of Harold S. Diehl.

ROBERT B. HOWARD, M.D., *Associate Dean*
GUEST EDITOR

Cerebrovascular Disease in General Practice

A. IANNONE AND A. B. BAKER*

University of Minnesota Medical School, Minneapolis

THE most common disorders of the nervous system involve the vascular system. Because of their frequency, these illnesses are encountered often in general practice. For many years, an indifferent medical attitude existed toward the cerebrovascular disturbances because of the feeling that treatment was not available and the outcome was predetermined. However, in recent years a great deal of study has been devoted to these illnesses and considerable new knowledge has accumulated concerning their diagnosis and treatment. A review of these newer studies would seem to be worthwhile in order to present some of the latest concepts regarding these diseases.

Cerebrovascular disorders often are secondary to some systemic process such as hypertension, diabetes, syphilis, polycythemia or purpura. Careful control of the primary condition can go a long way toward preventing or delaying cerebrovascular changes. Such a preventive approach, keeping in mind the possibility of cerebral complications, may well result in a decline in cerebrovascular disease and aid greatly in reducing the permanent residuals of brain damage.

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A. IANNONE

A. B. BAKER

Clinical Types of Cerebrovascular Disease

Clinically, and often pathologically, there are three different types of cerebrovascular disorders, namely, vascular insufficiency, intracerebral hemorrhage, and subarachnoid bleeding. In each type, specific etiologic factors are involved and a fairly constant group of symptoms allows for rapid and fairly easy recognition.

Vascular insufficiency impairs cerebral func-

tion temporarily or permanently. Symptoms appear rather suddenly and usually are focal in nature. They do not progress but tend to remain stationary or to regress. Generally, vascular insufficiency does not impair consciousness. The patient remains alert and comfortable in spite of the localized disturbance of cerebral function. The cerebrospinal fluid is normal.

Intracerebral hemorrhage also is sudden in onset and results in focal neurologic symptoms and signs. Generally, it is almost explosive in onset and produces evidence of severe brain damage. The patient is confused, lethargic or even comatose, and often has symptoms and signs of increased intracranial pressure with severe headache, vomiting, choked disk and evidence of medullary compression with changes in cardiac and respiratory function. Spinal puncture shows blood-tinged fluid. Prognosis is uniformly poor, the lesion proving fatal during the first week of illness in 75 per cent of cases.

Subarachnoid bleeding usually occurs in the younger age groups. It may also be very acute in onset, resulting in intense occipital headache, nuchal pain and rigidity, nausea and vomiting, drowsiness, mental confusion and, often, coma. The patient's age as well as the nuchal pain and rigidity help distinguish this condition from intracerebral hemorrhage. Spinal tap reveals very bloody fluid.

Etiologic Considerations

The etiologic factors involved in vascular diseases of the nervous system differ in the various age groups. A rapid survey of these etiologic factors may prove helpful in the final evaluation of the vascular process involved.

Infancy and childhood—Cerebrovascular disease is unusual in infancy and childhood. In most cases the process is a complication of some other pathologic condition.

Intracerebral as well as subarachnoid hemorrhage may complicate a large number of processes such as thrombopenic purpura, hemophilia, hemorrhagic disease of the newborn, and hypertensive states (coarctation of the aorta, chronic nephritis, pheochromocytoma), and may occur during convalescence from acute infections. Rupture of congenital aneurysms with subarachnoid bleeding is not seen in infancy but first appears in childhood.

Thrombosis is also unusual in infancy and childhood but has been reported following infectious diseases and in congenital syphilis and congenital heart disease. Venous sinus thromboses occur in dehydrated and chronically ill children who have foci of infection from adjacent regions such as the ears and nasal sinuses.

Embolic lesions to the cerebral vessels in infancy and childhood are most often associated with acute or subacute valvular disease of the heart. Occasionally, pulmonary suppuration will send emboli to the brain, causing obstructive symptoms that progress to show signs of sepsis.

Adolescence and youth—Embolic phenomena predominate as causes of cerebrovascular disease in this age group. In late adolescence, ruptured aneurysm is a frequent cause of subarachnoid bleeding. Intracerebral hemorrhage is extremely uncommon at this age, but cerebral thrombosis occasionally complicates some systemic vascular disturbance such as Buerger's disease, polyarteritis or lupus erythematosus.

Middle age—Vascular thromboses comprise the most common pathologic condition in this age group. Intracerebral vascular thromboses are seen principally in persons who have long-standing and fairly severe diabetes or hypertension. Cerebrovascular thromboses in the absence of such conditions are unusual. A number of thrombotic syndromes also implicate the extracerebral vessels in this age group, producing secondary ischemic changes within the nervous system. Two of the most common of these thrombotic processes involve the internal carotid artery and the posterior inferior cerebellar artery. The exact causes of these syndromes are not known but the prognosis in both is good. Polycythemia may play a role in cerebral thrombosis, and adequate treatment of this condition may prevent cerebral complications. Intracerebral or subarachnoid hemorrhage is uncommon in middle age and usually is associated with hypertension.

Old age—Any of the processes occurring in

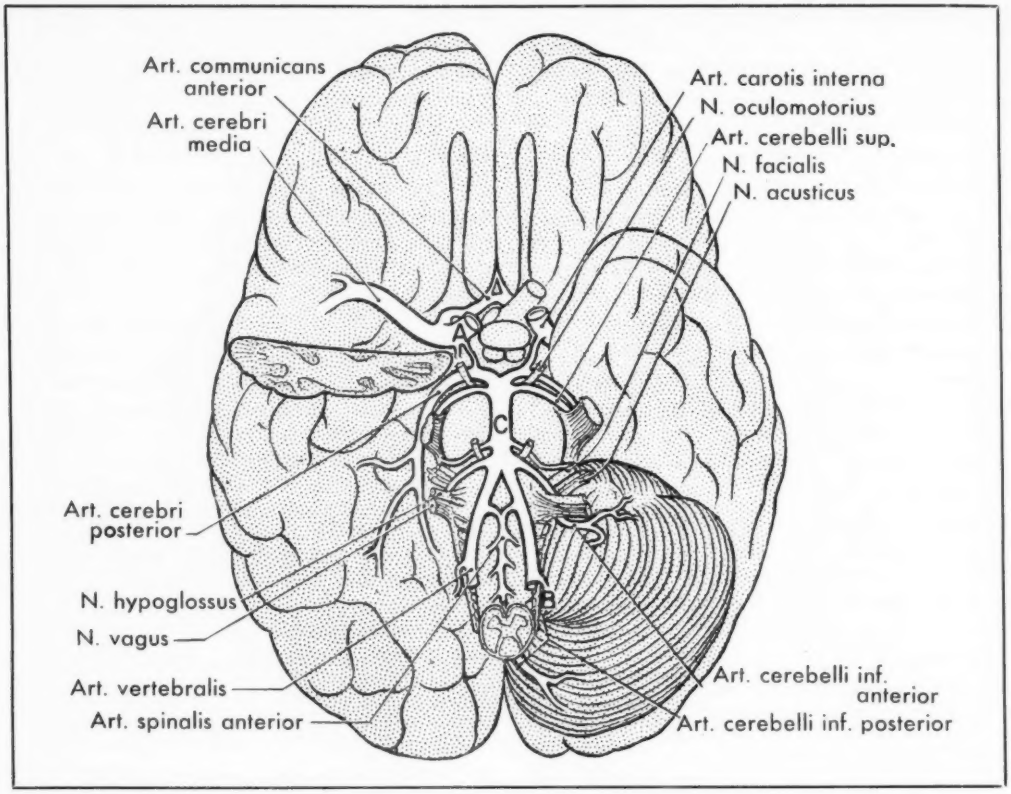

FIGURE 1. View of the base of the brain showing the circle of Willis.

A—Internal carotid artery, showing the possibilities for collateral circulation if this vessel is occluded.

B—Posterior inferior cerebellar artery, indicating its supply to the lateral surface of the medulla oblongata.

C—Basilar artery. Note its supply to both sides of the brain stem, giving bilateral symptomatology.

the middle age group may also occur in old age, but by far the most frequent cause of vascular disease in older persons is cerebral arteriosclerosis. When the arteriosclerotic process completely occludes the larger vessels, infarction of brain tissue results, with clinical evidence of cerebral deficit. The clinical picture depends on the vessels implicated. If a generalized narrowing of the smaller cerebral vessels has resulted in cerebrovascular insufficiency, the neurologic symptoms are more diffuse in nature and are precipitated by any factor that diminishes cerebral blood flow, such as a fall in blood pressure, cardiac failure, immobilization, or systemic infection. Hemorrhage is usually intracerebral in type in older persons, and often is secondary to a hypertensive state. Less commonly, it is due to rupture of a sclerotic vessel.

Specific Vascular Syndromes

There are a number of fairly specific vascular syndromes whose symptomatology is characteristic and which can be adequately treated. A brief review of them will aid in their recognition and therapeutic approach.

Thrombosis and insufficiency of internal carotid artery—This has become one of the most commonly recognized types of vascular disease in the middle and younger age groups.

Since each side of the brain receives a blood supply from both internal carotid arteries through the circle of Willis, the symptoms following occlusion of a single internal carotid artery depend on the efficacy of collateral circulation and the condition of the opposite internal carotid artery (figure 1, A). Young persons or those who have intact collateral circulation may have few or no symptoms from occlusion of a single internal carotid artery. In older persons the functional deficit may be severe. Since most persons have some collateral circulation, occlusion of a single vessel rarely produces severe symptoms.

Patients who have thrombosis and insufficiency of the internal carotid artery most commonly complain of some degree of unilateral muscular weakness or sensory disturbance. Speech involvement, chiefly manifested as expressive aphasia, is noted when the left internal carotid artery is implicated. Some patients may complain of episodes of transient blindness early in the disease, and a few may lose vision in one eye with primarily optic atrophy. These neurologic symptoms appear in distinct patterns. The so-called intermittent type is easily recognized and consists of recurring symptoms which usually duplicate the original episode. A series of such episodes may occur over a period of months or years, and if the condition is untreated the course will terminate in a strokelike incident with permanent residuals. In the apoplectic form of this illness, hemiplegia occurs suddenly without premonitory symptoms. The condition usually improves after a few days. The diagnosis should be considered when one sees a young person who has had sudden motor weakness and in whom one does not suspect involvement of the intracerebral vascular system. An absolute diagnosis can be made only by angiography.

Treatment—In the transient or intermittent type of insufficiency of the internal carotid artery, it is of the utmost importance to use anticoagulants before symptoms have become permanent. Once the thrombosis is complete, anticoagulants may be given to prevent further propagation of the thrombus toward the circle of Willis. Most patients under symptomatic treatment will improve and will be able to walk and carry out some limited activities.

Thrombosis of posterior inferior cerebellar artery—The posterior inferior cerebellar artery usually arises from the vertebral artery and supplies the lateral part of the medulla oblongata (figure 1, B). For some unknown reason, this vessel is very prone to occlusion in middle age. Clinical manifestations are very characteristic (figure 2). The onset is sudden, with severe vertigo and vomiting (eighth cranial nerve nucleus). There may be some pain and paresthesia of the ipsilateral side of the face associated with some loss of pain and thermal sensation on that side. In the typical case, superficial sensation is lost on the contralateral side of the body, producing the well-known dissociated anesthesia (one side of the face and opposite side of the body). Dysphagia due to involvement of pharyngeal and palatal muscles usually is transient and seen in the more severe cases. Ipsilateral incoordination implicates chiefly the upper extremity but may interfere with gait. In about two-thirds of the cases, Horner's syndrome (miosis and ptosis) is apparent on the side of involvement. In some milder cases, findings may be minimal. One should suspect the condition even when the syndrome is incomplete and only ipsilateral facial paresthesia, ipsilateral incoordination and vertigo are present. Glycosuria as well as albuminuria have been observed in this illness.

Prognosis and treatment—Prognosis usually is good, and most patients recover completely. However, there is always the risk that the thrombotic process may extend to implicate the vertebral artery, and the outcome then can be fatal. For this reason, all patients with thrombosis of the posterior inferior cerebellar artery should receive anticoagulants for at least three to six months. Under such a regimen, one can almost always anticipate an excellent recovery.

Insufficiency of basilar artery—The basilar artery is the only vessel in the intracranial cavity that singly supplies both sides of the brain, namely, the brain stem (figure 1, C). Partial or complete occlusion of the basilar artery is usually the result of arteriosclerosis in older persons. Complete occlusion leads to

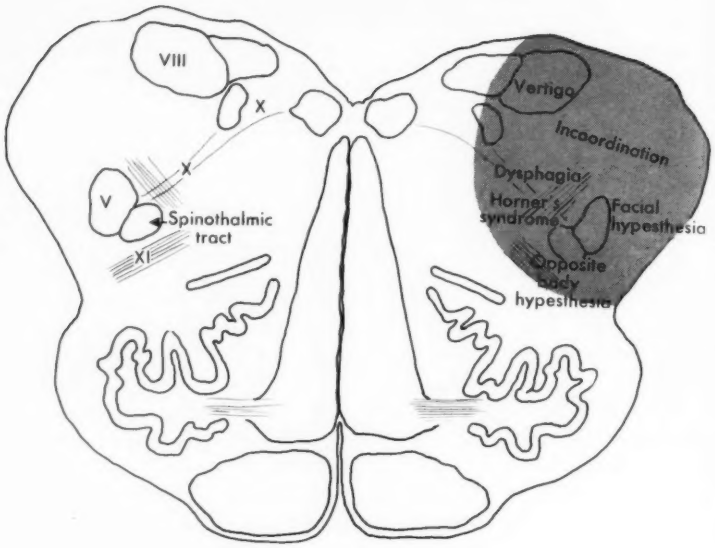

FIGURE 2. Cross section of the medulla oblongata to show the area implicated by occlusion of the posterior inferior cerebellar artery.

destruction of the brain stem and is rapidly fatal. However, it is possible to recognize partial narrowing of the vessel and thus institute therapy in an attempt to prevent complete occlusion. The characteristic symptoms of intermittent ischemia of this vessel are referable to the brain stem and consist of cranial nerve involvement associated with transient and shifting long-tract disturbances. Weakness or numbness may involve one limb or one side and may shift from side to side or limb to limb during different attacks. Visual disturbances are frequent and consist of dimness of vision and oculomotor disturbances with diplopia. There may also be transient episodes of vertigo, mental confusion, dysarthria or dysphagia. Sudden changes in position, particularly from the prone to the upright position, often precipitate attacks.

Prognosis and treatment—Prognosis in insufficiency of the basilar artery is poor, and complete occlusion will develop in many cases in spite of therapy. Treatment consists of administration of anticoagulants and should be maintained indefinitely. It has been our policy to use oral DICUMAROL®, keeping the prothrombin level at 15 to 25 per cent of normal by giving 50 to 100 mg. Dicumarol daily.

Subarachnoid hemorrhage—If one excludes such secondary forms of subarachnoid bleeding as those which follow trauma, hemorrhagic diseases and intracerebral hemorrhage, by far the most common cause of subarachnoid hemorrhage is rupture of an intracranial aneurysm. These aneurysms occur chiefly along the vessels of the circle of Willis and are seen most often clinically in the younger age groups. They may be silent for many years and first recognized by the dramatic appearance of symptoms and signs resulting from their rupture, when there is intense occipital pain of very acute onset followed almost immediately by confusion or loss of consciousness. Examination of the patient will reveal nuchal rigidity, and spinal puncture will reveal a bloody fluid. In some cases, rupture is preceded for years by unilateral transient retro-orbital headaches, always involving the same side of the head. Prognosis is very grave; 35 per cent of the patients die during the initial attack, and another 15 to 20 per cent succumb from a second bleeding episode within a period of weeks or months.

Some intracranial aneurysms may produce focal symptoms before they rupture. These symptoms consist chiefly of cranial nerve pal-

si s. For example, aneurysms of the internal c otid artery characteristically present with p osis, mydriasis and external squint (third cr nial nerve) of acute onset, occasionally accompanied by trigeminal nerve involvement or facial pain. Aneurysms of the anterior cerebral artery may produce anosmia, transient retro-orbital headache, and unilateral impairment of vision.

Treatment—During the acute phase, conservative treatment is indicated, with rigidly enforced bed rest and symptomatic therapy. As soon as recovery ensues, cerebral angiography should be considered to localize the aneurysm and determine whether or not it can be treated surgically. If the aneurysm is so located that surgical treatment is possible, this approach deserves consideration in view of the grave prognosis. If multiple lesions are present, if the aneurysm cannot be treated surgically, or if it cannot be visualized, the patient must be treated symptomatically. After recovery, he must be cautioned against all heavy lifting and severe straining.

Intracerebral hemorrhage and thrombosis—These processes occur chiefly in the older age groups. Theoretically, it should be easy to differentiate one from the other. One would anticipate that thrombosis would occur a little more slowly during periods of inactivity such as sleep. It should not give evidence of increased pressure such as headache, mental confusion or papilledema, and the cerebrospinal fluid should be normal. With cerebral hemorrhage, on the other hand, one would expect a very acute occurrence during activity, associated with headache, mental confusion, bloody cerebrospinal fluid, and signs of increased intracranial pressure.

Intracerebral hemorrhage and thrombosis frequently can be differentiated clinically, but this is by no means always the case. There is always a reasonable doubt as to the correct diagnosis because of the similarity of the clinical picture. This difficulty in making a positive distinction between hemorrhage and thrombosis plays an important part in therapy. There has been a tendency to recommend anticoagulant therapy for intracerebral thrombosis, but its value once a vessel is occluded certainly is questionable. Even more important is the danger of such therapy if the diagnosis is incorrect and a hemorrhagic process is present. For this reason, we have advised against anticoagulant therapy in all intracerebral processes where the exact diagnosis is in question. We have reserved the use of anticoagulants for thrombotic syndromes of the extracerebral vessels where the clinical manifestations leave no doubt as to the diagnosis.

A Critique of Operations for Peptic Ulcer

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OWEN H. WANGENSTEEN

MANY of the operations currently in use in the surgical management of peptic ulcer are outgrowths of the surgeons' wrestle with the problem of gastric cancer. The resection technics of Billroth for cancer were carried over into the surgery of peptic ulcer, and so similarly with gastrojejunostomy, which was first performed in 1881 in the Billroth clinic in Vienna by Wölfler[1] at the suggestion of his assistant, Nicoladani. Von Eiselsberg[2] originated the pyloric exclusion operation primarily as a palliative procedure for adherent antral gastric cancers, then considered inoperable. However, in his initial paper (1895), von Eiselsberg mentioned two instances in which the operation had been done for benign ulcer in the pyloroduodenal area.

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It may seem a bit strange, after all these years, that surgeons are still debating what the best operations are for the relief of peptic ulcer. Many groups in medicine are asking the same question. There is a persisting wide divergence of opinion even among surgeons who profess a special interest in management of peptic ulcer. In consequence, it is difficult to know what operation, if any, a physician should recommend for his patient who has failed to find complete relief under a conservative regimen.

Criteria of an Acceptable Operation

A number of items need to be considered in evaluating the likely promise of an operative procedure for a patient with peptic ulcer: (1) The operation should offer relief with reliable assurances of protection against recurrence. (2) The risk should be minimal. (3) The procedure should be unattended by undesirable side effects.

Any procedure that can give satisfying assurances on these three points can be recommended. However, no operation available today meets all these tests with a perfect score.

Pathologic and Physiologic Considerations

Duodenal ulcer is the most frequent and the most difficult to cure of the various manifestations of peptic ulcer. The ulcer diathesis finds its most zealous expression in duodenal ulcer. Uniformly, the gastric acidity is high and the peptic quality of the digestive juice also is great.

In gastric ulcer, on the contrary, the gastric juice almost invariably has acidity values in the lower range of normal and weak peptic digestive action—findings which more closely parallel the behavior of the normal stomach. In other words, it would appear that a mechanism which augments the secretory functions of the gastric parietal and the chief cells occasions the cause of duodenal ulcer, and that gastric ulcer is occasioned largely by local causes that undermine the resistance of the gastric epithelium to withstand the corrosive effects of a fairly normal acid-peptic juice plying over its surface.

Acid-peptic esophagitis, more commonly recognized now than in earlier years when it was known as idiopathic stricture of the esophagus, is perhaps better understood than are the origins of either duodenal or gastric ulcer. Situations that provide the opportunity for reflux of gastric juice into the esophagus are responsible for this manifestation of peptic ulcer. The squamous epithelium of the esophagus, defended by a very small number of mucus-secreting glands, cannot resist erosion by acid-peptic juice.

Gastric resection has been done in this clinic for so-called idiopathic esophageal stricture since 1939.[3] In fact, it was disappearance of strictures of the esophagus attending gastric resection that led subsequently (1944) to studies which demonstrated the great sensitivity of esophageal epithelium to injury by acid-peptic juice. Gastric resection reduces gastric secretory capacity and provides opportunity for ready gastric emptying—considerations that are very important in the relief of reflux esophagitis.

In instances of esophagitis occasioned by hiatal hernia, repair of the hernia and an adequate Heinekc-Mikulicz pyloroplasty succeed in alleviating the situation. A number of patients in this clinic who had extensive stricturing of the esophagus unattended by hiatal hernia obtained complete relief after gastric resection. In fact, no failures have been observed.[4] The relief provided by gastric resection, accompanied by occasional esophageal dilatation during the early weeks or months of convalescence, confirms the validity of the thesis that it is a satisfactory operation for acid-peptic esophageal stricture.

Methods of Evaluating the Promise of Operations

Empiricism of the surgeon—In the past, surgeons were wont to perform operations they believed would afford promise of relief from the ulcer diathesis and then sit back and wait to learn the results. This empiricism of the surgeon has been one of his besetting sins. Fortunately, surgeons of the present era, instructed by a keener interest in physiologic approaches, are not content to select operations on this type of evaluation alone. Elaboration of objective tests or hurdles which an acceptable operation must meet could provide many of the needed answers, supplanting as well as complementing the "wait and see" policy. The story of gastrojejunostomy and the strong expressions of confidence made for it by a large number of distinguished gastric surgeons over a period of four decades speak forcibly to this point. The death knell of gastrojejunostomy as an isolated procedure with which to attack peptic ulcer sounded long years ago.[5]

Protection against histamine-provoked ulcer—The histamine-in-beeswax implantation technic has proved very helpful in assessing the promise of operative procedures implemented to thwart the ulcer diathesis.[6] However, useful as it has been, time has shown that it too needs the corroboration of auxiliary aids in probing the protection of operations against recurrent ulcer. In the dog, tubular resection appeared to afford satisfactory protection against ulcer provoked by histamine in beeswax;[7] yet, in man, tubular resection has not lived up to that promise, which

suggests that a single test, however rigorous, may not be enough.[8]

Isolated canine Heidenhain pouch studies—Another technic of assessing the protection of an operation proposed for peptic ulcer in man is that of noting the responses attending the ingestion of meat in isolated canine gastric pouches following performance of the operation under scrutiny. This technic, much in use 30 years ago[9,10] and only revived in recent years, has given helpful information on certain operative procedures and detected weaknesses of others. It is noteworthy that it helped uncover one of the defections of tubular gastric resection.[11]

Studies of sensitivity of esophageal mucosa—More recently in this clinic, advantage has been taken of the great sensitivity of the esophageal mucosa in evaluating the worth of operative procedures directed at the ulcer diathesis. Some years ago (1948), attention was directed to the ease with which esophageal perforation could be produced in the experimental animal by perfusing the esophagus with acid-peptic juice.[12] More recently, this method has been invoked to assess the promise of operations as well as to determine prior to operation the potential digestive capacity of the gastric juice of patients who have ulcer. It has also proved valuable as a diagnostic tool by providing evidence of the secretion of a gastric juice of high digestive power in cases in which a duodenal ulcer is suspected but repeated x-ray studies fail to reveal its presence. In patients having pain alone, unattended by any of the ordinary complications of peptic ulcer, the diagnosis is, as every clinician knows, rarely made today without x-ray confirmation. Overnight secretions are recovered from the stomachs of such patients by an indwelling gastric tube attached to a source of suction. Perfusion studies on the cat's esophagus are made with the gastric aspirate, and esophageal perforation within two hours after commencement of the perfusion suggests the presence of an undiagnosed duodenal ulcer. Operation undertaken in several patients with unrecognized ulcer disability of long standing confirmed the presence of duodenal ulcer, substantiating the findings of esophageal perfusion.

Critical Follow-up Studies

The "wait and see" policy alone is inadequate to determine the promise of an operation. Yet, the worth of careful follow-up studies critically made must not be minimized. Such observations can be very important. In fact, no study of the protection of operations for peptic ulcer in man is complete without the helpful guidance of critical clinical evaluation. Such follow-up studies would seem to indicate that there are two operations that afford real promise in the management of duodenal ulcer: (1) segmental resection and (2) hemigastrectomy with a complemental vagotomy. Strangely enough, in experimental animals hemigastrectomy and vagotomy failed to protect against ulcer provoked by histamine in beeswax. Yet, the results reported recently by a number of groups suggest definitely that this operation affords protection against recurrent ulcer in man.

Viewed from any standpoint, segmental resection appears to be a particularly satisfactory operation. It protects against ulcer provoked by histamine in beeswax. Studies on isolated gastric pouches of dogs, noting the responses attending ingestion of meat following segmental gastric resection, suggest that it is an acceptable procedure. Esophageal perfusion studies on the gastric aspirate of patients who have undergone segmental resection indicate that this group of patients should do particularly well.[13]

Segmental resection has stood the test of time and would appear to be one of the best operations to combat duodenal ulcer in man. An additional strong point in its favor is that it is easy to perform and avoids the technical hazards of the Billroth II procedure in difficult and low-lying duodenal craters. The only question which needs to be resolved concerning segmental resection is how large the resection should be. As figure 1 suggests, we have performed segmental resection of three orders of magnitude: (1) a 75 per cent resection in which the fundic remnant constitutes approximately 10 per cent of the entire stomach, (2) a 50 per cent resection (hemigastrectomy) in which all of the antrum (20 per cent of the

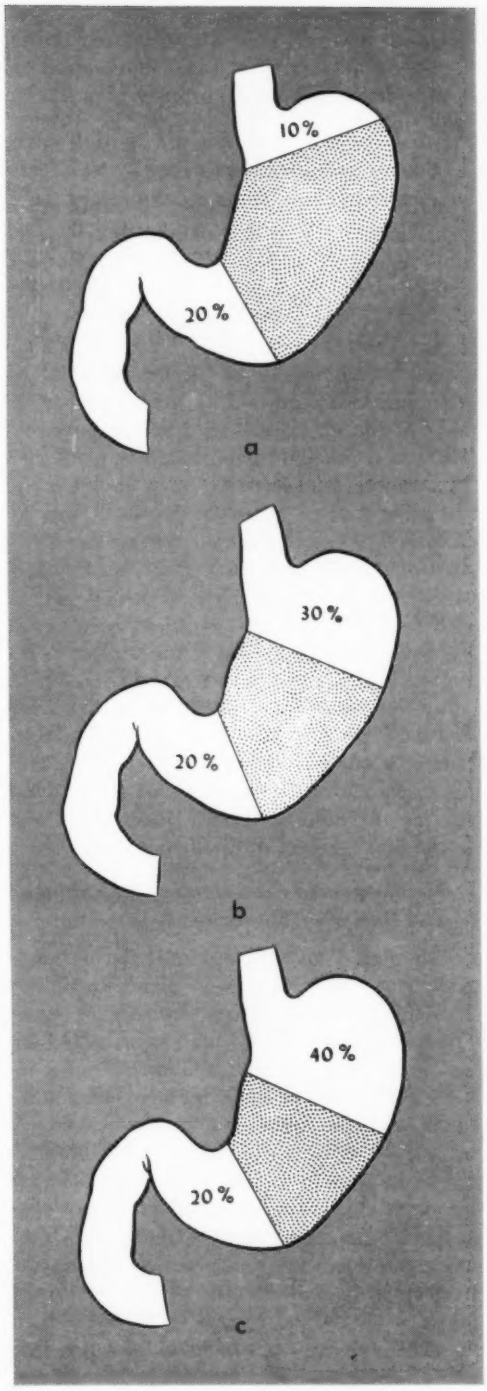


FIGURE 1. Extent of segmental resection. An adequate pyloroplasty is added routinely to assure satisfactory gastric emptying. (See figure 4.)

a. The large segmental resection (70 to 75 per cent) is larger than it needs to be. Dumping is rather frequent. Recurrence has not been observed. The incidence of achlorhydria after histamine is high (87 per cent). The digestive power of the night secretions tested on the cat's esophagus is low.

b. The moderate segmental resection (50 per cent) represents the likely optimal size of resection. No recurrence has been observed. Dumping is rare. Achlorhydria of aspirated night secretions is high (76 per cent); achlorhydria after triple histamine stimulation is 53 per cent. Digestive power of gastric juice is unusually low. Excision represents approximately 60 per cent of the acid-secreting area.

c. Following the small or 40 per cent resection, dumping does not occur. Fasting achlorhydria as well as achlorhydria following histamine stimulation is less consistent than after the moderate (50 per cent) segmental resection. Persistent high digestive action of gastric juice in a few patients suggests that the extent of this operation may be inadequate to protect fully against recurrent ulcer.

entire stomach) and a 30 per cent residual fundic pouch are left, and (3) a 35 to 40 per cent resection in which the antrum (20 per cent) and a proximal pouch constituting about 40 per cent or a little more of the entire stomach are left. The large segmental resection (94 cases) was performed between 6 and 10 years ago. There have been no recurrences. Our experience suggests that when the antrum is left, it is safe to leave a residual proximal fundic pouch a little larger than that left in the conventional three-quarter Billroth resection. Exactly how much more acid-secreting area may be left remains to be determined. Preliminary studies by Salmon and Perry[13a] on the digestive power of the gastric juice secreted by operated stomachs suggest that the midsegmental gastric resection, leaving a proximal pouch constituting 25 to 30 per cent of the entire stomach, is within the range of the optimal size of the resection.

A complemental pyloroplasty is added routinely inasmuch as transverse gastric division vagotomizes the antrum and pylorus, thereby interfering with the gastric emptying. My associate, Dr. Donald J. Ferguson of the Veterans Administration Hospital, finds in preserving the vagal innervation to the pyloro-antral area that pyloroplasty is unnecessary.[14] The

observations of Thal et al.[11] (1957) would suggest, however, that failure to free the pylorus and antrum from vagal innervation can compromise the curative promise of segmental resection.

Proximal Gastrectomy for Peptic Ulcer

A few European surgeons[15,16] within recent years have advocated proximal gastric resection for duodenal ulcer. In 1951, I[17] advocated such a procedure in the surgical management of mega-esophagus, and in more recent years (1953, 1957) it has been abandoned for an amplified Heller extramucosal myotomy accomplished by inflation of a balloon in the management of cardiospasm.[18,19] Moreover, when I undertook complete excision of the acid-secreting area in the surgical correction of mega-esophagus, it was not known that sacrifice of all the acid-secreting area of the stomach resulted in megaloblastic anemia—too high a price at which to purchase relief from any condition, save cancer of the stomach.[20,21] And if the surgeon electing such an operation to treat duodenal ulcer left a very small area of acid-secreting tissue and sacrificed the esophagogastric juncture, his patient would eventually suffer from esophagitis. Certainly no surgeon is warranted in disrupting the esophagogastric juncture in man in the management of duodenal ulcer.

Vagotomy and Complemental Drainage and Resection Technics

Vagotomy has a long and discontinuous history in the management of peptic ulcer.[22] It remained for Dragstedt and his associates to explore in a thorough and systematic manner the protection it afforded in combating the ulcer diathesis. Their studies have contributed much valuable information on the behavior of the vagotomized stomach in man and dog.[23]

Vagotomy as an isolated procedure failed because the vagotomized stomach cannot empty readily. Vagotomy accompanied by a drainage operation such as gastrojejunostomy or pyloroplasty, in the hands of its ardent proponents, has been followed by an over-all recurrence rate of approximately 10 per cent within five years.[24,25] Nevertheless, vagotomy accompanied by drainage procedures continues to have strong supporters. A number of those who defend such an operation do so on the thesis that if the operation fails one can carry out a resection subsequently. It is not illogical to conclude that any procedure that carries so high a recurrence rate does not merit the serious attention of the profession.

A number of current reports would indicate that the recurrence rate following distal hemigastrectomy (Billroth II) complemented by vagotomy is virtually nil.[26,27] If, on the contrary, gastric resection of the same magnitude is done with a Billroth I type of restoration, the recurrence rate is like that of the Billroth II three-quarter resection unaccompanied by vagotomy.[27,28]

My experience with vagotomy is very limited. Bilateral subdiaphragmatic vagotomy was done in two patients in this clinic prior to 1940.[29,30] Mears'[31] subsequent observation (1943) of incomplete control of night secretion in heavily atropinized patients with duodenal ulcer gave little encouragement to explore the promise of vagotomy in thwarting the ulcer diathesis. Failure of hemigastrectomy and vagotomy to protect against ulcer provoked by histamine in beeswax in the dog suggested that it was an inadequate operation for duodenal ulcer.[32] My experience with a number of patients who successively have had gastrojejunostomy, vagotomy, gastric resection and additional gastric resections confirmed the impression that vagotomy, though affording protection, did not add the necessary assurance which so-called intractable ulcer patients needed.[33] Proponents of vagotomy and hemigastrectomy, too, have alluded to this contrasting behavior of the procedure carried out as a primary and a secondary operation.

With these experiences in mind, I have preferred to observe the evaluation of vagotomy and complemental resection technics in the hands of other surgeons. It is very reassuring, therefore, to have a number of recent enthusiastic reports indicating the effectiveness of hemigastrectomy and vagotomy in thwarting recurrent ulcer.[26,27] Certainly, removing the neurogenic and hormonal sources of stimulation of gastric secretion meets the demands of

a physiologic method of controlling the ulcer diathesis.

Smithwick's[26] group of observers (1957) report a very low incidence of undesirable side effects, such as dumping and loss of weight, attending the performance of hemigastrectomy and vagotomy. The Mount Sinai group, Colp[34] and associates, report a higher incidence of undesired side effects and postoperative complications in patients having a complemental vagotomy than in similar Billroth II resections unaccompanied by vagotomy.

Defection of the Billroth I Operation

The importance of a critical follow-up period of observation in deciding the worth of an operative procedure finds ample proof in the surprise defection of the Billroth I operation. It would appear that, granted a resection of comparable size, the Billroth I procedure should have distinct advantages over the Billroth II operation. However, adequate corroboration of the failure of the Billroth I procedure to provide protection against recurrent ulcer has come from a number of sources (Ordahl and associates,[35] 1955, Boston; Goligher et al.,[36] 1956, Leeds, England; Wallensten,[37] 1957, Ørebro, Sweden). In fact, these three investigative groups reported recurrences of 18 per cent, 17 per cent and 11 per cent, respectively, attending employment of the Billroth I operation in the management of duodenal ulcer. On the contrary, the same groups, and others, reported recurrence rates of 2 to 4 per cent accompanying the Billroth II procedure. Physiologically, it would appear that following a three-quarter gastric resection nature's way of end to end restoration would have definite advantages. The contrary proves to be the case: Terminolateral gastrojejunal restoration with a blind afferent duodenojejunal loop is followed by a much smaller incidence of recurrent ulcer. The reasons for this difference are not apparent.

Von Haberer,[38] who was the keenest exponent of the Billroth I procedure over a long period of years, gave up the operation some years before he withdrew from the surgical scene. For many years, he performed a terminolateral gastroduodenostomy in doing the Billroth I operation in an attempt to elude the problem of gastric juice plying over a scarred duodenal mucosa.[39] He found that this device also failed to protect against recurrence.

Another possibility is that the smaller stoma of the Billroth I operation may be responsible for prolonged retention of food within the residual gastric pouch, thereby augmenting gastric secretion, even in the absence of the antrum. On this score, it should be remarked that recent studies in our laboratory failed to detect in canine Heidenhain pouches any suggestion of an important difference in secretion following the Billroth I procedure whether the stoma was large or small.[40] However, surgeons who have been partial to the Billroth I procedure noted that a frequent site of recurrence was in the residual gastric fragment, a circumstance definitely suggesting obstruction as a causative factor.[35,36] Earlier investigators have suggested occasionally that, following loss of the antrum, a gastrinlike effect from contact with food may be provoked from the fundic segment of the stomach.[41,42] If true, the superiority of the larger stoma for the Billroth I operation is obvious.

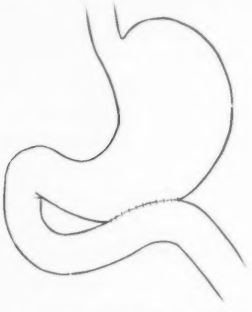
Another possible conclusion is that, in the absence of the antrum, the presence of acid-peptic juice in the duodenum augments gastric secretion. This thesis deserves experimental inquiry. An earlier study from this clinic indicated that excision of the duodenum was followed by augmented gastric secretion.[43] Similar studies need to be done with the antrum removed. Still another possibility not to be overlooked is that the first few centimeters of the duodenum, the most frequent site of all peptic ulcers, may, like esophageal mucosa, have a lower threshold of sensitivity to injury by acid-peptic juice, particularly after loss of the antrum.*

Answers to some of these queries will have to be supplied to provide satisfying reasons

*This writer believes it is delivery of an active acid-peptic juice with a low pH, in an area of the duodenum relatively unprotected by neutralizing fluids inasmuch as bile and pancreatic juice flow forward normally and are not constantly regurgitated in a retrograde direction to bathe the new gastric outlet—that it is this circumstance which accounts for failure of the Billroth I operation for duodenal ulcer.

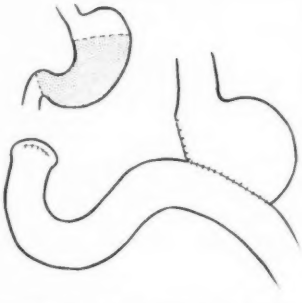
FIGURE 2. Present status of operations in light of experimental and clinical studies.

a to f. Resection procedures.

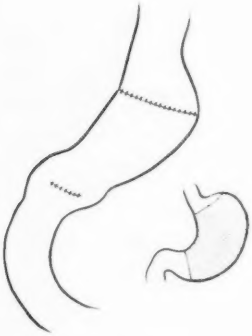


a. *Gastrojejunostomy.* Poor. Obsequies pronounced a number of years ago.[5]

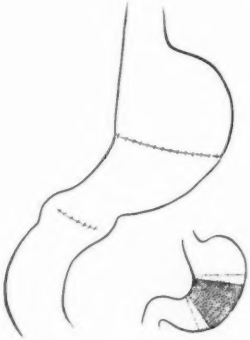
b. *Billroth I (75 per cent).* Poor. Undesirable in duodenal ulcer because of high incidence of stomal ulcer (11 to 18 per cent). Reason for high recurrence rate not known. Satisfactory for antral ulcer.



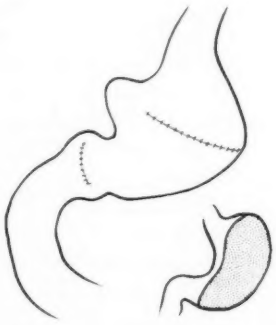
c. *Billroth II (75 per cent).* Good. Recurrence rate 2 to 4 per cent. To be avoided in difficult duodenal ulcer craters because of increased operative risk. Dumping often severe. Weight loss usual.



d. *Large segmental resection (75 per cent) with adequate pyloroplasty.* Excellent. No recurrences in 6 to 10 years. Low operative risk. Applicable in all peptic ulcers save the antral ulcer. Dumping and weight loss are usual but less than in Billroth II. Applicable to all but antral ulcers.



e. *Smaller segmental resection (40 to 60 per cent) with adequate pyloroplasty.* Excellent. No observed recurrence in one to three years. Low operative risk. Little dumping. Weight reduction minimal. Longer period of follow-up necessary for final decision regarding size of optimal resection. A moderate (50 per cent) resection would appear necessary to assure high incidence of achlorhydria and low digestive power of gastric juice. Small resection (40 per cent) may be inadequate to afford adequate protection against recurrent ulcer.

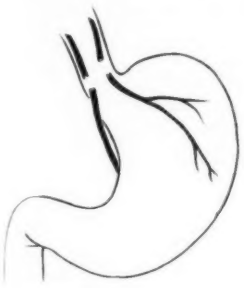


f. *Tubular resection (75 per cent).* Fair. Recurrence rate 3 per cent (three to six years). Low operative risk. Reasons for recurrences not wholly known, but probably owing to (1) failure to denervate antrum, (2) retention of food and prolonged contact with antral mucosa in tent-like pocket on lesser curvature.

for the defection of the Billroth I operation.

The anemic spot on the anterior duodenal wall described by W. J. Mayo[44] in 1908 has been emphasized by surgeons for half a century. Von Haberer, despite many disappointments with the Billroth I procedure, continued to employ it in duodenal ulcer through a long and active surgical career, but came ultimately

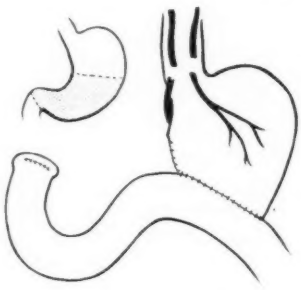
g to j. Vagotomy procedures.



g. *Vagotomy.* Poor. Stomach fails to empty. Followed by occurrence of gastric ulcer in man and animals.

h. *Vagotomy and drainage operation (gastrojejunostomy or pyloroplasty).* Fair. High recurrence rate (10 per cent). Low operative mortality. High recurrence rate suggests little justification for performance.

i. *Vagotomy and hemigastrectomy, Billroth I.* Good. Recurrence rate unknown, probably in area of 4 per cent.



j. *Vagotomy and hemigastrectomy, Billroth II.* Excellent. No observed recurrences. Should not be employed in technically difficult duodenal ulcers.

(1939) to abandon it because of the high recurrence rate. The reasons are not clear; the situation needs to be studied particularly with reference to abetting causes that may potentiate the susceptibility of duodenal mucosa to injury by acid-peptic juice.

It has become very obvious to all gastric surgeons that small variations in procedure believed to have little or no physiologic significance may however lead to important differences. Because hidden meanings lurk not uncommonly in the premises that we accept, only crucial experiments which test those assumptions or time itself can determine whether they are true or false. The unanticipated contrasting behavior of the Billroth I and II procedures with reference to recurrence of ulcer in man is certainly a case in point. And so similarly with segmental and tubular gastric resection: It would appear that protection against recurrent ulcer in these two latter procedures should be approximately the same; experimental inquiry and time cooperated to indicate the superiority of segmental resection.

Inadequacy of the Small (40 to 50 Per Cent) Billroth II Resection

Distal hemigastrectomy as an isolated operation carried out on the Billroth II plan of procedure also proved inadequate to combat the ulcer diathesis, as every student of the subject knows. Finsterer,[45] writing of the surgical management of peptic ulcer in 1923, advocated following the line of the spinal column in removing the distal segment of the stomach. When he re-examined the results of such procedures in 1934,[46] he found the operation did not afford adequate protection against recurrent ulcer. He then advised a two-thirds resection, elevating the line of resection on the greater curvature to a more proximal point. Heuer and associates,[47] in their monograph on peptic ulcer, concluded that the ultimate results of gastrojejunostomy and the Billroth II hemigastrectomy, performed for peptic ulcer, were not very different. They found that the over-all accomplishment of gastrojejunostomy

TABLE 1

ANALYSIS OF OPERATIONS ON MAN ON BASIS OF CRITERIA PROPOSED FOR EVALUATION OF SUCCESS

OPERATION	INCIDENCE OF RECURRENT ULCER AFTER OPERATION (PER CENT)	OPERATIVE MORTALITY (BASED ON ULCER OPERATION AS PRIMARY PROCEDURE) (PER CENT)	UNDESIRABLE SIDE EFFECTS
Gastrojejunostomy	15-40	0.5-2	Good*
Billroth I (75 per cent)	11-18	2-4	Fair
Billroth II (75 per cent)	2-4	2-4	Fair to poor
Large segmental resection (75 per cent)	0	2	Fair
*Moderate segmental resection (50 per cent)	0	0 > 1.6	Good
Small segmental resection (40 per cent)	0	0	Very good
Tubular resection	3	2	Fair to good
Gastrojejunostomy and vagotomy	10	0.5-2	Good
Vagotomy and hemigastrectomy (Billroth I)	1-4	2-4	Good
Vagotomy and hemigastrectomy (Billroth II)	0	2-4	Good

*Dumping first decided by Mix (1920) after gastrojejunostomy.

very closely approached that of hemigastrectomy. There was not more than a 10 per cent advantage for the latter procedure, with a better mortality score for gastrojejunostomy.

Technical Advantages of Segmental Resection in the Difficult Duodenum

Figure 2 and tables 1 and 2 supply summary data which concern the pertinent items relating to operations currently employed in the management of peptic ulcer. Note that only two operations are accompanied by high scores on the basis of protection against recurrent ulcer: the large segmental resection and the Billroth II hemigastrectomy accompanied by vagotomy. Whereas recurrences have not yet been observed in the smaller segmental resections (35 to 50 per cent) over a one to three year period, obviously a longer time must elapse before one can speak with assurance on this point.*

One advantage of segmental resection is simplicity of performance with a very low operative risk.[8,48] The only manifestation of peptic ulcer for which the procedure cannot be employed is the antral ulcer. In several instances of ulcer of the pyloric canal (almost invariably on the posterior wall), I have excised the ulcer down to the pyloric muscle for purposes of biopsy and reconstituted mucosal continuity by a few coaptation sutures when a frozen section indicated that the lesion was benign. A conventional segmental resection completes the procedure.

In difficult duodenal ulcer craters, there would appear to be an important advantage in avoiding the Billroth II procedure, namely, eliminating the hazard of a leaking duodenal stump as well as damage to the pancreas with ensuing pancreatic necrosis. In instances of duodenal ulcer in which the duodenum is not readily mobile, the segmental procedure has a wider range of application and is a safer operation than hemigastrectomy accompanied by vagotomy.

Complications of Peptic Ulcer and Operative Indications

Perforation—In this clinic more than 20 years ago (1935), eight patients with perforated ulcer were treated with an inlying gastric tube attached to suction.[49] The method was abandoned when a patient with a large duodenal perforation succumbed attending its use. That occurrence antedated the sulfona-

*Recently, a patient who initially had a 40 per cent segmental gastric resection for a stomal and a gastric ulcer following a gastrojejunostomy was found to have a recurrent ulcer. The situation was corrected by performing a Billroth II operation.

mi[illegible] and antibiotic eras. Even today, a large pn[illegible]moperitoneum attending ulcer perforatio[illegible] should be considered a contraindication to [illegible]he nonoperative management of perforatio[illegible]. The method of choice in management of per[illegible]forated peptic ulcer in this clinic continues to [illegible]e surgical closure of the perforation. In a number of clinics, simultaneous gastric resection has been done. In this clinic, experience with primary resection in perforation has been small. For perforated duodenal ulcer, if primary resection is to be done, I would prefer segmental resection. For perforated antral ulcer, if primary resection is contemplated it should consist of one of the Billroth procedures. For any ulcer at or above the infundibulum on the lesser curvature, a segmental resection can readily be done. The operative mortality of closure of perforated ulcer in this clinic has been zero over a number of years.

Obstruction—Obstruction is seen largely in instances of juxtapyloric ulcers, more frequently in duodenal ulcer than in antral ulcer. Ordinarily a perforating type of lesion that provokes thickening of the serosal tissues occasions it. In fact, *in forme fruste*-type perforations, in which early sealing occurs, I have on more than one occasion observed lamination of an onion-peel type of serosal overlay at the site of the penetration of the ulcer through the duodenal wall.

Hemorrhage—Hemorrhage is the most frequent cause of death from peptic ulcer, accounting for more than 50 per cent. It is obvious, therefore, that adequate control of the acid-peptic ulcer diathesis is necessary to lower the mortality from ulcer.

Routine early surgical intervention has had a good trial in the hands of Stewart and associates[50] (Buffalo, 1956) and Enquist et al.[51] (Brooklyn, 1957). I have been wont to believe, without having had the opportunity to

TABLE 2

EVALUATION OF RESPONSES TO VARIOUS OPERATIONS BASED ON ADDITIONAL CRITERIA

OPERATION	SPONTANEOUS ULCERS IN DOGS (PER CENT)	HISTAMINE-IN-BEESWAX ULCER (PER CENT)	RESPONSE OF ISOLATED CANINE HEIDENHAIN POUCHES TO FEEDING 200 GM. HORSEMEAT	DIGESTIVE POWER OF GASTRIC JUICE (OVERNIGHT ASPIRATION IN MAN) ON ESOPHAGEAL PERFUSION IN CAT	ACHLORHYDRIA (MAN) AFTER HISTAMINE STIMULATION
Gastrojejunostomy	6	100	Increased		0
Billroth I (75%)	0	0	0	Low	High
Billroth II (75%)	0	0	0	Low	High
Large segmental resection (75%)	0	0	0	Very low	High (90%)
Moderate segmental resection (50%)	0		Low	Low	Moderate (57%)*
Small segmental resection (40%)	0		Low	Usually low	Low (37%)
Tubular resection	0	0	Increased	Often increased	Low
Vagotomy and gastrojejunostomy	0	100		?	Low
Vagotomy and hemigastrectomy (Billroth I)	0	50			High
Vagotomy and hemigastrectomy (Billroth II)	0	50			High

*Incidence of achlorhydria in unstimulated overnight aspirations was 73 per cent.

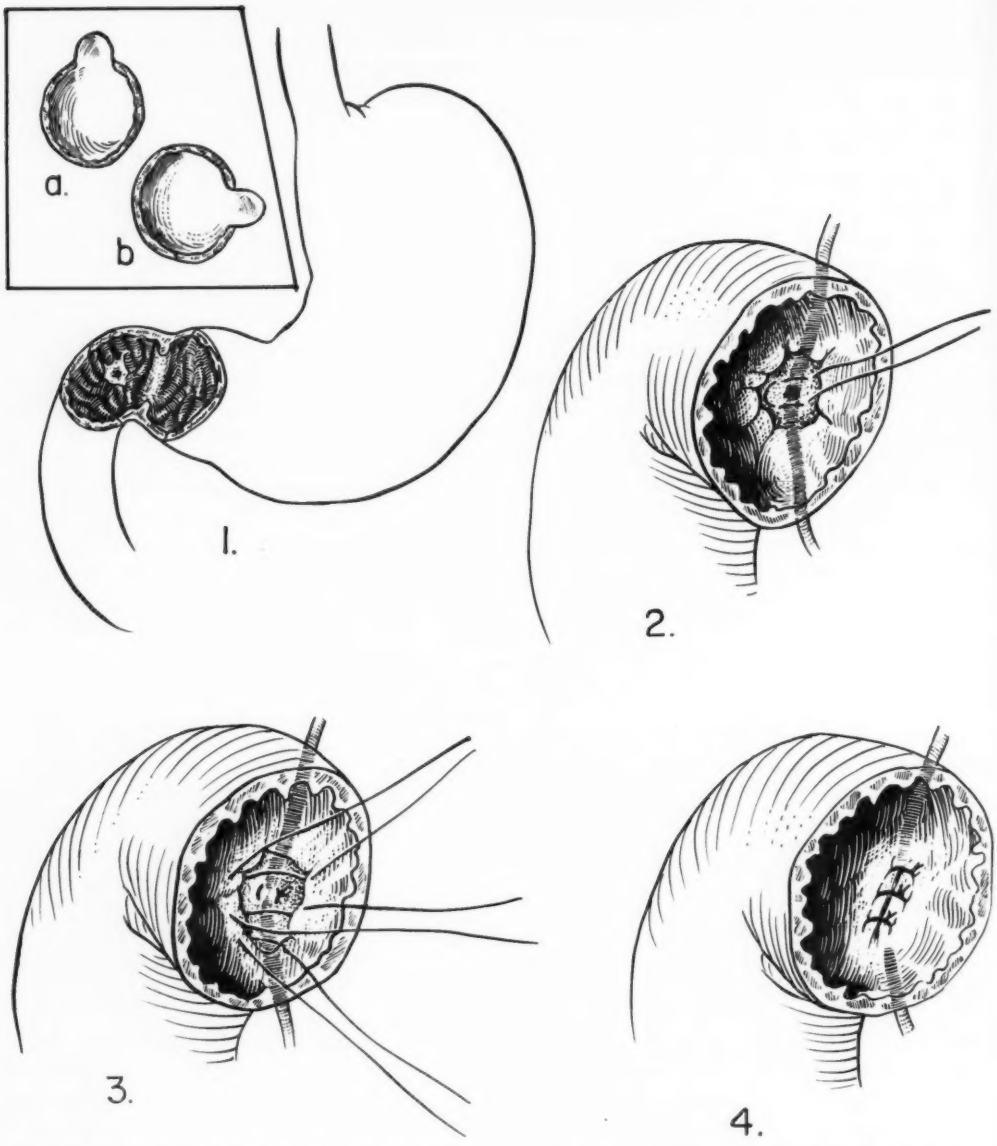


FIGURE 3. The technic of dealing with a duodenal ulcer crater in segmental resection.

1. A fairly typical postpyloric duodenal ulcer crater.
   a. A supraduodenal ulcer crater occurring at 12 o'clock. When such a crater penetrates the thickness of the intestinal wall, the perforation extends out over the common bile duct.
   b. In this location, the ulcer crater may extend into the pancreas.
   Craters in these locations may be difficult to deal with by either of the Billroth operations; the crater shown in insert *a* constitutes an especially difficult technical problem for the surgeon. Segmental gastric resection is a far simpler technic of dealing with this technically difficult problem.
2. Placement of a "horseshoe" stitch about the bleeding vessel in an ulcer crater.
3. Technic of sliding the mucosal surfaces over the crater. It is not necessary to undercut the mucosa to complete the closure.
4. The completed suture.

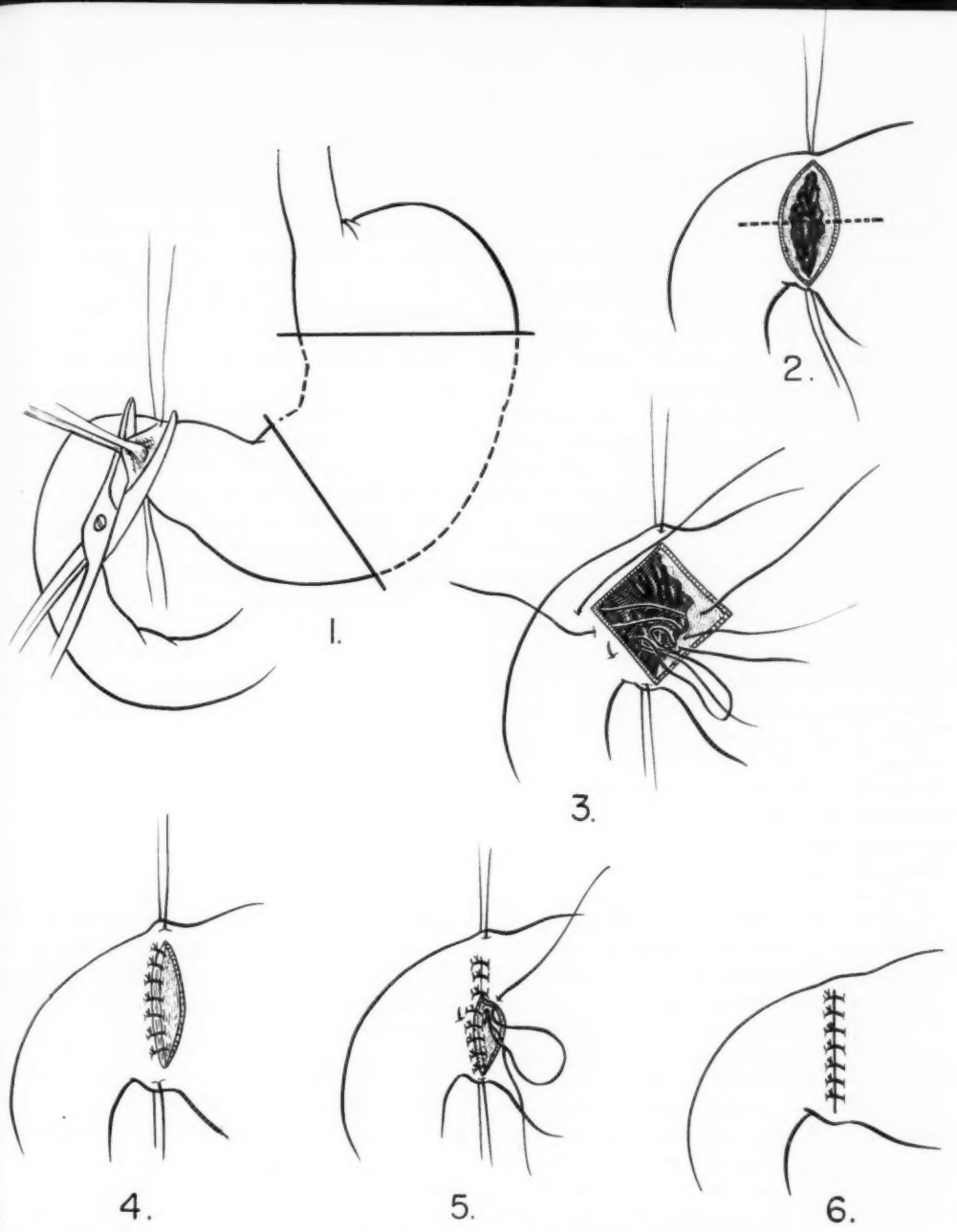


FIGURE 4. Technic of pyloroplasty to avoid the "dog-ear" problem of the Heineke-Mikulicz pyloroplasty closure.

1. The anterior wall of the duodenum is lifted with an Allis clamp, and the anterior portion of the pyloric sphincter is partially cut away.

2. In the midportion of the resulting ellipse, a short extension is made in both directions in the gastroduodenal axis.

3. Closure of the resultant incision. The first suture of catgut approximates gastric mucosa and the full thickness of the duodenal wall.

4. First row of sutures tied.

5. The seromuscular wall of the gastric flap glides over the first suture line.

6. The completed closure.
The surgeon accustomed to the Heineke-Mikulicz type of pyloroplasty will be gratified to see how simply this incision closes. This pyloroplasty incision also permits inspection of the duodenum and distal portion of the antrum.

test the thesis, that early surgical intervention would lower the mortality from massive gastric hemorrhage. However, the reports of Stewart and Dennis and their associates serve to temper such a suggestion, in that their results are not better than the results in clinics where the decision of whether or not to operate has been made on the merits of the case, operation being undertaken in those instances in which hemorrhage continues.

One reason for the high mortality reported by such groups is that operation is of necessity undertaken under somewhat unfavorable circumstances. Moreover, the worst hemorrhages, apart from instances in which the patients have portal hypertension, are from deep duodenal ulcer craters. This condition is notably difficult to deal with even in elective operations and has continued to constitute a large segment of the operative mortality in Billroth II operations. On this score, it should be said that segmental resection with an accompanying pyloroplasty presents distinct advantages. A long linear slit through the anterior wall of the pylorus extended into the lower antrum and for a short distance through the anterior duodenal wall suffices to expose any bleeding duodenal ulcer crater. Placement of a single stitch about the bleeding vessel usually controls hemorrhage. Mucosal apposition is readily obtained by merely sliding the adjacent mucosal surfaces together with three interrupted sutures of fine silk. My residents and I have carried out this procedure a number of times, and it has proved eminently satisfactory. Closure of the pyloroplasty incision is far simpler than dealing with a difficult duodenal ulcer crater in the Billroth II operation. If advocates of early surgical intervention for hemorrhage were to employ segmental resection, I believe the operative mortality would decrease considerably. (Figures 3 and 4.)

In 1945 and again in 1950, I[52, 52a] advocated empirical resection for massive gastric hemorrhage accompanied by hematemesis and reported a number of successful operative interventions. In more recent years, this suggestion has come to be widely adopted. Spencer and Maloney[53] (1956) prefer a 7 in. linear gastrotomy incision to locate the source of the bleeding. When operating for gastric hemorrhage, segmental resection with pyloroplasty almost invariably has sufficed to indicate the source of bleeding when this has been obscure. Even in instances in which an ulcer was not seen or felt by external examination of the duodenum or visualized from within, I have occasionally observed a stream of cherry-red blood projected upward for a distance of 40 cm. on incising the duodenum, an occurrence that indicates the bleeding is essentially arteriolar in origin. Such hemorrhage, however, from an occult source, in my experience has more frequently had its origin in the stomach, most commonly in a small erosion high up on the lesser curvature slightly posterior to the attachment of the gastrohepatic omentum.

There are isolated instances of hemorrhage in which the source is very difficult to determine or localize at operation. In cases of grave hemorrhage where the source of bleeding is not readily apparent at operation, a linear slit is made in a segment of the stomach that would subsequently be excised in segmental resection. Large clots of blood, if present, are evacuated, and a gauze pack is inserted through the pylorus; another is inserted into the esophageal hiatus, and a third is left in the stomach. Efforts are made meanwhile to keep the stomach sucked out. Use of gauze in this manner can serve as a means of determining quickly the source of hemorrhage under trying circumstances when the bleeding is brisk enough to threaten exsanguination.

Elective Resection for Complications of Ulcer

All complications of ulcer are evidences of an uncontrolled ulcer diathesis. Recurrent hemorrhage is in itself an indication for implementation of more definitive control. It is common procedure in this clinic to admit to the hospital for overnight gastric aspiration patients whose perforated ulcers have been closed. If the aspirated digestive juice causes perforation of the cat's esophagus on perfusion, resection is advised.[54] Inasmuch as obstruction is owing essentially to a sealed type of perforation in which layering of laminations of the serosal tissue leads to narrowing

of the pyloroduodenal lumen, such ulcers too should be looked on as candidates for operation, even though obstruction relents under intragastric dripping of skim milk.

Esophageal Varices

No satisfying method is yet available to combat massive hemorrhage from actively bleeding esophageal varices in portal hypertension. Current practice in most clinics is to try to staunch hemorrhage with an inlying gastric balloon that will exert pressure on the bleeding vessels, and then to effect reduction of portal pressure by performing a portacaval shunt as soon as feasible. When compressive technics fail to arrest hemorrhage, placement of running catgut sutures in the esophageal mucosa is the procedure that probably has had widest usage. In a few cases in this clinic, the distal 5 to 7 cm. of the esophagus, from which area the bleeding most frequently originates, has been excised, together with the entire acid-secreting area of the stomach; total gastrectomy also has been done.[52a] Merendino and Dillard's[55] jejunal interposition operation, accompanied by excision of the lower reaches of the esophagus and the upper segment of the stomach, would appear to be a satisfactory procedure and one that will not eventuate in megaloblastic anemia, as does an extensive proximal gastrectomy.

High gastric transection, as advocated by Tanner[56] (1954), undoubtedly has some merit in diminishing the threat of hemorrhage, but, as I[52] learned in performing such a procedure together with a 90 per cent distal gastric resection, it is inadequate to afford continuing protection from the esophageal bleeding of portal hypertension.

In the portal hypertension of cirrhosis, portacaval shunts have proved more effective in the hands of most surgeons than has the splenorenal shunt. Blakemore[57] (1957) believes that after establishment of a large portacaval anastomosis a large spleen will shrink in size, making it unnecessary to excise it to eliminate hypersplenism. Dubuque, Mulligan and Neville (1957)[57a] believe that a portacaval shunt potentiates the ulcer diathesis.

For the extrahepatic blocks in the portal vein, excision technics such as those devised by Phemister and Humphreys[58] (1947), Merendino and Dillard[55] (1955) and this writer[52, 52a] (1945, 1950) continue to be the operative procedures of choice.

The Factor of Stress

The importance of stress in the genesis of peptic ulcer is becoming better understood. Zubiran and associates[59] (1952) believe that factors of stress fail to augment gastric secretion following vagotomy. Seymour Gray and associates[60] (1953), on the contrary, insist that the stress factor acts directly on the parietal cell and is therefore uninfluenced by either vagotomy or excision of the antrum. A postganglionic sympathectomy (excision of the mesenteric ganglia) potentiates the ulcer diathesis.[61] Peptic ulcer also has been reported in man following preganglionic sympathectomy. It would appear, therefore, that denervation of the adrenal fails to protect against the stress ulcer. In fact, Elliott[62] (1915), Mann[63] (1917) and others have noted the occurrence of ulcer following excision of the adrenals in dogs. Fatigue, anoxia, cold, fat embolism, hemorrhage, severe trauma, formidable operations, burns, infections—all represent stress situations.[52] The stress of operations augments the peptic activity of gastric juice. Experiments under way in this clinic[64] suggest that stress factors may abet the ulcer diathesis too, by lowering the threshold of resistance of tissue to injury by acid-peptic juice. What is the stress factor in duodenal ulcer? It would be good to know. Where the source or nature of the stress remains unknown, the only effective remedy would appear to be an operative procedure which would make the ulcer diathesis nonassertive.

Resurrection of Antral Exclusion

As already indicated, von Eiselsberg[2] designed antral exclusion in 1895 to relieve obstruction in inoperable gastric cancer and to circumvent the technical difficulty of dealing with the adherent pyloroduodenal ulcer. Von Haberer[39a] spoke with restrained enthusiasm of antral exclusion before the German Surgical Congress in 1913. In 1918, Finsterer[45a]

re-emphasized the worth of the procedure in dealing with difficult duodenal ulcers, pointing out that the mucosa in the antral segment could be excised to eliminate the gastrin factor. In 1926, Willmanns[65] indicated that when the antral exclusion operation was done it was mandatory to excise the antral mucosa. In his original description of the procedure, von Eiselsberg[2] suggested division and inversion of the antrum proximal to the lesion in the distal stomach which could not be removed. Rauch[66] (1952) found that the recurrence rate following antral exclusion for duodenal ulcer in this clinic, when accompanied by a three-quarter gastric resection, was no greater than that following the conventional three-quarter resection; however, the mucosa was regularly excised before the seromuscular antral cylinder was closed.

As early as 1923, Smidt[9] of Jena had observed in dogs with isolated Heidenhain pouches that the pyloric-exclusion operation was accompanied by hypersecretion attending the ingestion of food, a finding confirmed by Enderlen and Zukschwerdt[41] in 1931. In fact, all gastric surgeons gradually came to adopt the thesis that antral exclusion is a nonphysiologic operation for duodenal ulcer and consigned it to the limbo of the forgotten and undesirable. Von Haberer[39] definitely gave up the operation in 1921 because of an incidence of stomal ulcer of 20 per cent, and in 1923 Smidt published objective proof of the hypersecretion induced by the operation. The only reason that so many years intervened before antral exclusion fell completely from grace is that conflicting papers concerning the procedure continued to appear until approximately a dozen years ago. Now, Waddell and Bartlett[67] of Boston would have us believe that if antral exclusion is accompanied by hemigastrectomy and truncal vagotomy, it is quite an acceptable operation for the difficult duodenal ulcer. In fact, Waddell has performed the operation in the laboratory as well as in man, and recommends it as an operation of election.

Sauvage and Harkins and their co-workers[68] observed in 1953 that antral exclusion, in which the antrum is attached to the esophagus, was followed quite regularly (100 per cent) by jejunal ulcer, despite the concomitant performance of vagotomy. However, these workers did not perform hemigastrectomy simultaneously. When Kelly, Cross and I[69] performed antral exclusion with vagotomy in dogs, interestingly enough no jejunal ulcers occurred. The procedure was carried out in six animals. When antral exclusion was combined with an 80 per cent gastric resection, stomal ulcers occurred in 42 per cent of the dogs studied (5 to 12 animals).*

Dragstedt and associates have done a great deal to emphasize the hypersecretion that attends transplantation of the antrum,[70] especially when it is placed on the colon. My[48] defense of segmental resection was posited on the belief that there was an important difference between *retention* and *exclusion* of the antrum. I believe, therefore, that the profession should accept with considerable reservation the suggestion of Waddell that antral exclusion accompanied by hemigastrectomy and vagotomy is an acceptable procedure for duodenal ulcer. If the experience of the past has shed any helpful light on the ulcer-potentiating capacity of antral exclusion. I believe it is correct to suggest that Waddell's sanguine hopes for the procedure will probably end only in disappointment.

Summary and Conclusions

Available operations aimed at the relief of the peptic ulcer diathesis are assessed from the following points of view: (1) protection against recurrent ulcer, (2) operative mortality, and (3) freedom from undesirable side effects.

In light of current evidence, only two operations appear to meet these criteria in an acceptable manner: (1) segmental resection and (2) hemigastrectomy performed in the Billroth II manner.

Definition of objective criteria by which operations can be assessed without prolonged empirical testing in man is, of course, highly

*In a more recent series of experiments in which antral exclusion was combined with hemigastrectomy (Billroth II) and vagotomy, the observed incidence of spontaneous gastrojejunal ulcer was 10 per cent in four months. Within this time, large perforated stomal ulcers had developed in 2 of 19 dogs.[64]

desirable. Three technics to adduce evidence to guide the surgeon have been employed in this clinic: (1) assessment of the protection afforded by a given operation against ulcer provoked by histamine in beeswax; (2) response to ingestion of meat observed in isolated Heidenhain pouches in dogs after performance of the operation under scrutiny; and (3) digestive power of the gastric juice aspirated from the stomachs of patients who have undergone the operations.

In this clinic, we have had little or no experience with the role of vagotomy procedures in thwarting the peptic ulcer diathesis. However, it is quite apparent from the literature that, in practiced hands, drainage operations such as gastrojejunostomy when complemented by truncal vagotomy are attended by a recurrence rate of approximately 10 per cent. The reports of Smithwick and associates (Boston) and Edwards and associates (Nashville) indicate that hemigastrectomy performed on the Billroth II plan of operation and complemented by vagotomy is unattended by recurrent ulcer.

In this clinic, the large segmental gastric resection (75 per cent) was done in 94 cases between 6 and 10 years ago. Each of the patients has been carefully followed, and no recurrent ulcer has been observed in this group. This experience suggests that a lesser segmental operation may prove adequate. Our present experience with the lesser segmental resection is yet too brief in years to speak with any suggestion of finality. However, it would appear from studies made on the digestive power of gastric juice aspirated from the stomachs of patients who have undergone midsegmental gastric resections of about 50 per cent of the total stomach that such operations will in all likelihood protect against recurrent ulcer. Lesser segmental resections representing approximately 35 per cent of the entire gastric area may be inadequate to protect against recurrent ulcer, for the incidence of achlorhydria following administration of histamine to these patients is not as high as it is in instances of larger segmental resections.[13a] Moreover, the digestive power of gastric juice is not lowered consistently in the same way as it is in the large segmental or in hemigastrectomy.

If a three-quarter resection performed on the Billroth II plan of operation is adequate to protect against recurrent ulcer, inasmuch as preservation of the antrum in continuity with the gastric pouch affords additional protection, it is safe to conclude that something less than the conventional three-quarter resection is in order. Since the antrum constitutes approximately 20 per cent of the total gastric area, it is obvious that in the conventional three-quarter gastric resection on the Billroth plan of operation approximately 80 per cent of the acid-secreting area is excised. In performing a 50 per cent segmental resection, leaving the antrum, approximately 70 to 75 per cent of the acid-secreting area is excised. In other words, in addition to salvage of the antrum (20 per cent of the stomach), segmental resection, because of the protection afforded by the antrum, makes it permissible to leave approximately an additional 5 to 10 per cent of the acid-secreting area. The total salvage is therefore around 25 to 30 per cent over the conventional Billroth II three-quarter resection. In other words, a gastric resection that constitutes just less than a hemigastrectomy seems to be an adequate operation. These circumstances combine to make segmental resection an acceptable operation from the patient's point of view. The syndrome of gastric dumping attending the lesser segmental resection is observed far less commonly than in more aggressive excisions.

In performing segmental gastric resection for a patient with a duodenal ulcer crater, it is important to approximate the duodenal mucosa by a few stitches over the defect—an item which is easily achieved through the pyloroplasty incision. Inasmuch as a transverse division of the stomach proximal to the antrum invariably vagotomizes the pylorus, it is mandatory always to perform pyloroplasty to facilitate gastric drainage and emptying. This is one of the circumstances which accounted for failure of segmental resection in the hands of German surgeons 50 years ago. In fact, I had to learn the lesson independently when I took up with the operation approximately 10 years ago.

Segmental resection presents the advantage over hemigastrectomy with vagotomy that it avoids the hazards of the difficult duodenal ulcer. In fact, segmental resection is adaptable to all types of peptic ulcer save the antral.

The reasons for failure of the Billroth I procedure are not obvious. Von Haberer, the most ardent advocate of the operation for almost two decades, finally gave it up because of the high recurrence rate. He attached blame for its failure to the belief that the acid-peptic juice continued to ply over an area where healing of the ulcer had resulted in a scar without complete regeneration. The nature of the defection of the Billroth I procedure is not adequately or satisfactorily explained as yet. This writer inclines to the belief that delivery of an active acid-peptic juice into a segment of the duodenum, relatively unguarded because of a low level of back flow of bile and pancreatic juice into the most proximal segment of the duodenum—that this is the primary cause for the failure of the Billroth I operation.

Finally, the persisting large mortality from peptic ulcer, owing essentially to failure of medical management to protect against hemorrhage, indicates that better control of the peptic ulcer diathesis demands that operation should be resorted to more frequently than has been done in the past. The only known means to overcome the peptic ulcer diathesis is an adequate operation which will protect against ulcer recurrence.

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Tranquilizing and Related Drugs; a Guide for the General Physician

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THE tranquilizing agents available today facilitate control and management of many nervous and mental disturbances in a way not possible formerly. Because of the need for such therapy, these agents have reached a degree of popularity seldom if ever achieved before. The first tranquilizer appeared on the United States market late in 1954, yet in 1956 these drugs held four of the first 10 places in prescription sales.[1]

Of the new preparations appearing each month, many are advertised for treatment of nervous tension and related symptoms. Some vary only slightly from existing drugs; some are new tranquilizers, some are new sedatives, and some are neither. It is therefore a problem for the practicing physician to become familiar with these preparations, let alone to keep perspective in the field.

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WILBUR BENSON

The vagaries and complexities of the psychiatric field complicate the matter further. A fair amount is known about the first tranquilizing drugs, but it will be years before we fully understand how these products act and which ones are best for which conditions. Although we know that the new preparations are not all alike and many are definitely promising, for the most part their advantages, limitations and efficacy are yet to be determined.

FIGURE 1. Depression of cortical activity, directly or indirectly, by the older sedatives and hypnotics.

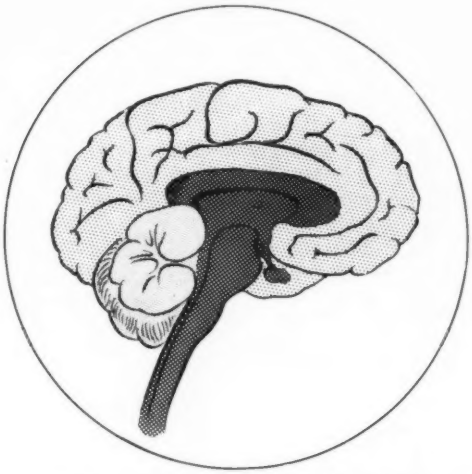


FIGURE 2. Relative absence of cortical depression by the tranquilizers.

Definition of Tranquilization

Tranquilization is somewhat different from sedation. Sedative agents affect the cortical as well as the subcortical areas in the brain (figure 1). In contrast, the tranquilizers act principally on the lower brain areas (figure 2). Their tranquilizing effect may be described as the production of emotional calmness and relaxation without significant sedation, hypnosis, motor impairment or euphoria; and yet they characteristically produce some sedative effect, particularly in certain persons and if large doses are used. This sedative effect, however, differs from that of the regular hypnotic drugs. It is more transitory, and even when deliberately fostered by the utilization of large doses, such as might be done to control an excited patient, it is not of the same depth or quality. To illustrate, a previously excited patient who is now tranquilized may sleep readily and for long periods, but he is easily awakened. When awake, his eyelids may droop and he may appear somewhat "doped," but he is mentally clear, rational and cooperative and has relatively good motor coordination. He is usually calm and reasonable and may have good insight into the fact that he recently was disturbed and upset. This remarkable change in demeanor and attitude could not have occurred with the drugs previously available. If barbiturates were given in sufficient quantities to control such an excited patient, he would be so sedated that he could not function adequately either mentally or physically. Further, to continue giving large amounts of barbiturates would be hazardous, whereas relatively heavy administration of most tranquilizing agents usually can be continued over a period of months if necessary.

Tentative Classification

A classification of tranquilizing drugs and other agents affecting human behavior is of practical and academic importance. Like other attempts at classification,[1-19] this also may be incomplete and tentative.

In this tentative classification, the groupings are largely based on clinical effect. Chemical and pharmacologic factors have played a more dominant role in determining the subgroupings. With most compounds, a fair degree of correlation exists between the clinical action and the chemical and pharmacologic properties. We hope this classification will give the physician some perspective of the relationship of the various compounds. It may also serve as a background for preliminary appraisal of new agents as they appear. Since the physician cannot always depend on the

TABLE I

MAJOR TRANQUILIZERS

a. Phenothiazine Group

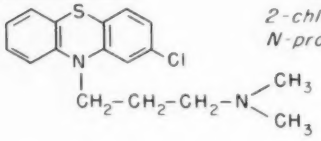
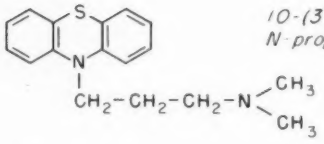
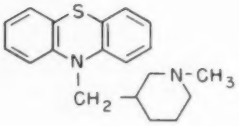
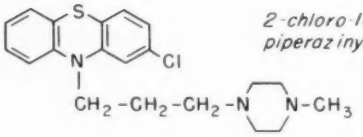
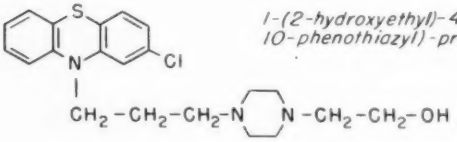
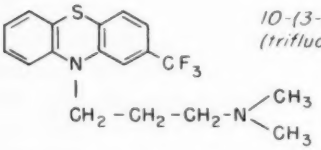
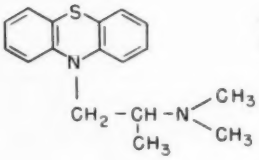
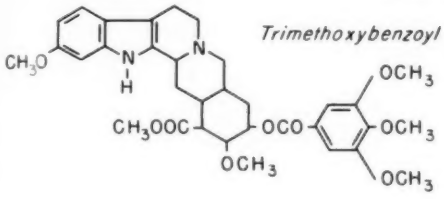
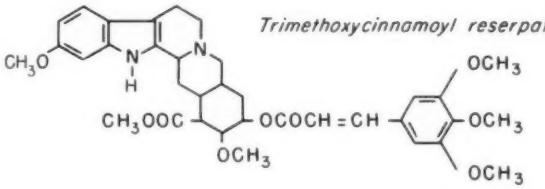
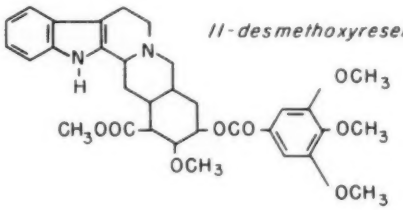
STRUCTURE	CHEMICAL NAME	GENERIC NAME	TRADE NAME
	*2-chloro-10-(3' dimethylamino-N-propyl) phenothiazine*	*Chlorpromazine*	Thorazine
	*10-(3-dimethylamino-N-propyl) phenothiazine*	*Promazine*	Sparine
	*N-(1-methyl-3-piperidyl methyl) phenothiazine*	*Mepazine*	Pacatal
	*2-chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine*	*Proclorperazine*	Compazine
	*1-(2-hydroxyethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine*	*Perphenazine*	Trilafon
	*10-(3-dimethylaminopropyl)-2-(trifluoromethyl) phenothiazine*	*Trifluprom azine*	Vesprin
	*N-(2 dimethylamino-1-propyl) phenothiazine*	*Promethazine*	Phenergan

TABLE I

MAJOR TRANQUILIZERS (continued)

b Rauwolfia Group

STRUCTURE	CHEMICAL NAME	GENERIC NAME	TRADE NAME
	*Trimethoxybenzoyl reserpate*	*Reserpine*	Serpasil
	*Trimethoxycinnamoyl reserpate*	*Rescinnamine*	Moderil
	*11-desmethoxyreserpine*	*Deserpidine (Reconescine)*	Harmonyl

claims that accompany the introduction of new therapeutic agents, he should be guided by the pharmacology of the drug and by carefully controlled clinical studies. Merely knowing an agent's chemical name and formula may enable the physician to classify it. A new drug that is similar to others will probably have the dominant action of that group. On the other hand, minor chemical changes in a compound can result in therapeutic differences of considerable practical importance. For example, the slight substitution of a methoxy (OCH_3) group for a hydroxy (OH) radical on the morphine molecule changes the compound from a potent narcotic to the weaker and less addicting analgesic codeine. Likewise, in the field of tranquilizers a minor chemical modification can make an important difference in potency, action and side effects.

Major Tranquilizing Drugs

Table 1 lists the major tranquilizing drugs. Their distinguishing characteristics are:

1. These drugs produce emotional calmness and mental relaxation, as was previously described.

2. They are highly effective in controlling the symptoms of acutely and chronically disturbed psychotic patients.

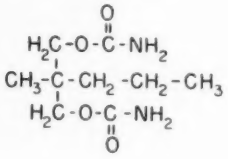
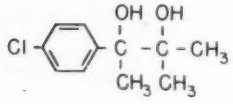
3. They are capable of producing the reversible "extrapyramidal" syndrome characterized by rigidity, tremors and drooling.

4. The incidence of annoying side reac-

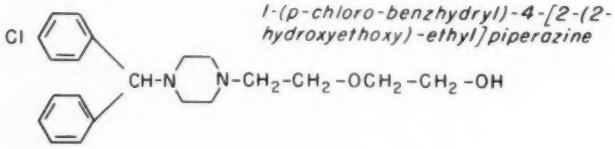
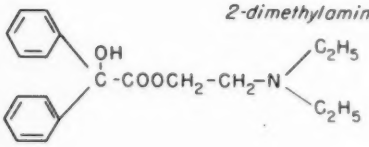
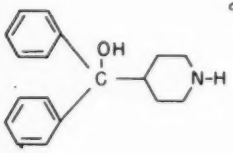
TABLE II

MINOR TRANQUILIZERS

a. Alkanediol Type

STRUCTURE	CHEMICAL NAME	GENERIC NAME	TRADE NAME
	2-methyl-2-n-propyl-1,3-propanediol dicarbamate	Meprobamate	Miltown Equanil
	2-p-chlorophenyl-3-methyl-2,3-butanediol	Phenaglycodol	Ultran

b. Diphenylmethane Type

	1-(p-chloro-benzhydryl)-4-[2-(2-hydroxyethoxy)-ethyl]piperazine	Hydroxyzine	Atarax
	2-dimethylaminoethyl benzilate	Benactyzine	Suavitil
	α-(4-piperidyl) benzhydrol	Azacyclonol	Frenquel

tions is relatively high with the use of these drugs, and serious dangers do exist to some extent.[10, 11]

5. They produce little if any dependency or habituation.

The major tranquilizers are the drugs of choice in excited, delusional or disorganized states, including those of toxic and organic origin. Chronically or severely incapacitated psychoneurotic patients, many of whom are ambulatory schizophrenics, often fail to benefit from the minor tranquilizers but may be helped by one of the major tranquilizers.

The first six drugs listed in table 1 are phenothiazine tranquilizers now on the market. It has already been demonstrated that

some of them are more potent than chlorpromazine and have a different spectrum of action. Almost certainly, many other compounds will join this group in the next few years. Many of these undoubtedly will prove to be major tranquilizers of potency equal to or greater than the drugs listed here. Others may prove much less active as tranquilizers. Nevertheless, they are tentatively included in the group of major tranquilizers because of their close chemical relationship. PHENERGAN®, long known as an antihistaminic, is included on the basis of preliminary reports of its usefulness as a tranquilizer. Perhaps others of a related group of compounds will also fit in the tranquilizing category.

Of the 16 or more known alkaloids found in Rauwolfia plants, reserpine, rescinnamine and deserpidine are on the market for clinical use. Reserpine appears under many brand names, as virtually every pharmaceutical house has this alkaloid on the market. Likewise, the purified extract of the whole Rauwolfia root appears under many brand names (RAUWILOID®, RAUDIXIN®, etc.).

Minor Tranquilizing Drugs

Table 2 lists the minor tranquilizers. Their distinguishing characteristics are:

1. These drugs produce calmness or relaxation but not of the same quality as the major tranquilizers.
2. They are useful in treatment of psychoneurotic problems and common nervous tension but are not highly effective in treatment of disturbed psychotic patients.
3. They do not produce the extrapyramidal motor phenomena so characteristic of the major tranquilizers.
4. The incidence of annoying side reactions with the use of these drugs is relatively low. Dangerous reactions are rare.
5. Habituation may occur with the use of some of these agents.

The minor tranquilizers are the preferred drugs in the common nervous states. Because of their relative safety, many physicians prefer to try them first in any ambulatory case. Their calming action is usually sufficient to benefit the majority of persons with nervous tension, mild depression, psychosomatic disorders, and the like.

Meprobamate has been sufficiently studied to determine that it meets the criteria listed for the minor tranquilizers. Less is known about phenaglycodol, but from the data available it appears similar to meprobamate. The autonomic suppressants hydroxyzine and benactyzine are also placed in this same general class, as judged from the data available. The ataractic azacyclonol (FRENQUEL®), which is chemically related to these latter drugs, also may belong in this group.

New Nonbarbiturate Sedatives and Calmatives

The group of drugs represented by those listed in table 3 are referred to collectively by some as psychosedatives. We have included them in this discussion largely because many of them have only recently appeared on the market. Because of the advertising accompanying them, they may be readily confused with the tranquilizers. Most of these drugs have not been studied sufficiently to know their advantages and disadvantages. To date, the smoothness, safety and potency claimed for them have not been shown to hold any great advantage over the older sedative medications. However, they do provide the physician with a variety of drugs from which to choose and which can be used for the occasional patient who cannot tolerate the barbiturates or chloral hydrate. At present, it is our opinion that the physician would do well to

TABLE 3

THE NEW NONBARBITURATE SEDATIVES AND CALMATIVES

GENERIC NAME	TRADE NAME
Methylparafynol	DORMISON®
Ethinamate	VALMID®
Glutethimide	DORIDEN®
Methyprylon	NOLUDAR®
Ethchlorvynol	PLACIDYL®
Petrichloral	PERICLOR®
Ectylurea	NOSTYN®
Oxanamide	QUIACTIN®

consider these drugs as sedatives rather than tranquilizers.

Antidepressive Drugs

Table 4 presents a group of drugs with which the tranquilizers recently have been associated. The first five are widely advertised for relief of mild psychologic depression. Possibly they have slight value in such cases, but they are of little or no value in treatment of serious depression, in which electroshock therapy and other such measures still are necessary. These drugs, however, are still very useful in overcoming drowsiness associated with the administration of major tranquilizers. Most of them are relatively safe. Pipradrol and methyl-phenidylacetate are virtually free from unpleasant side effects and thus offer a practical advantage over the amphetamines in psychiatric use.

Iproniazid is entirely different from the first five drugs in this group. Its antidepressive action, presumably due to its amine oxidase-inhibiting activity, appears promising. It is relatively new and its potentiality for harmful effects will need to be watched.

Drug Combinations

Adding to the confusion of the great number of new drugs recently introduced are the dozens of varying combinations now appearing on the market. Most of these are aimed at saving the physician trouble by providing ready-made combinations. Table 5 lists some examples.

Relatively new sedative preparations also may consist of combinations of standard barbiturates. We mention them here because they can be readily confused with tranquilizing agents. Examples are NIDAR® and ETHOBRAL®.

TABLE 4

ANTIDEPRESSIVE DRUGS

GENERIC NAME	TRADE NAME
Amphetamine	BENZEDRINE®
Dextro-amphetamine	DEXEDRINE®
Methamphetamine	METHEDRINE®
Pipradrol	MERATRAN®
Methyl-phenidylacetate	RITALIN®
Iproniazid	MARSILID®

TABLE 5

DRUG COMBINATIONS

TRADE NAME	DRUGS COMBINED
ATARAXOID®	ATARAX® and steroid
DEXAMYL®	Dexedrine and amobarbital
MILPREM®	MILTOWN® and conjugated estrogens
NEMBUSERPIN®	NEMBUTAL® and SERPASIL®
PATHIBAMATE®	PATHILON® and meprobamate
SERPATILIN®	Serpasil and Ritalin

Principles of Clinical Application

The newness of the field, the variations of clinical situations, and individual responsiveness leave much to trial and error. However, a few general principles are becoming evident.

The pharmaceutical house marketing a given product offers the physician a dosage schedule which varies with the condition being treated. While this schedule may be effective for the most part, the physician will do well to remember that tranquilizing agents are, in themselves, essentially symptomatic remedies. They provide symptomatic relief better than did the older medications.

One principle is to give enough medication to ameliorate or control the symptoms and to maintain the medication at this dosage level long enough to allow a more fundamental readjustment to occur. This assumes that side effects do not interfere. Much psychiatric treatment aims at fostering natural healing by removing emotional obstructions through psychotherapy, environmental manipulation, and the like. When tranquilizing drugs render a person calm and reasonable, he will be in a better position to work out his problems. This supporting action may be likened to the bacteriostatic effect of a modern antibiotic.

As a second principle, it is clear that all other indicated therapeutic measures should be instituted concurrently. Otherwise, the beneficial effects of the drug are apt to be temporary and to last only as long as it is administered. Only after the patient's improvement has become stabilized for a few weeks should

the medication be withdrawn and then it should be done cautiously and gradually.

In treating ambulatory patients, minor tranquilizers administered according to recommended directions usually are sufficient to control symptoms without producing undue sedation or other side effects. For the simpler nervous reactions which the practicing physician commonly encounters, this normalizing effect of the medication plus reassurance and counseling may suffice to effect recovery from the episode. The physician's personal interest and his ability to counsel the patient in confidence on personal as well as strictly medical matters remain as important as ever. The tranquilizing drugs do not eliminate the need for these components, although they do help the process along.

In treatment of chronically nervous ambulatory patients, and others somewhat more severely ill, it is usually necessary to increase the dosage until the symptoms are controlled, or possibly to use a major tranquilizer. All other treatment procedures that are practical should be set into operation, and it may be necessary to continue the treatment program for several months to give the patient time and opportunity to work through his problems. The benefits accruing from the addition of tranquilizing agents to the treatment program may offer enough additional relief to allow the patient to function at a more adequate level. Some patients will need to remain on tranquilizing medication in much the same way that an epileptic patient needs to stay on anticonvulsant drugs.

Psychiatric emergencies handled by general physicians include delirium, acute manic or schizophrenic excitements, and the like. Parenteral administration of one of the phenothiazines may control the symptoms promptly. Rapid build-up of the medication, possibly to a high level, may be necessary. The danger in short-term therapy with the phenothiazines is very little greater with a larger dose.

Senile persons are prone to agitated or disturbed states that formerly were difficult to control. The major tranquilizing drugs, particularly the phenothiazines, are highly efficacious in relieving much of the restlessness, paranoid reactions and other signs of emotional distress in these cases. Although the associated enfeeblement and intellectual decline remain, such patients more readily accept the necessary supervision and management. Small doses are well tolerated and usually are all that is required.

Chronic psychotic patients, formerly seldom seen by general physicians, are now being released from state and other institutions in significant numbers. Most of them are only in partial remission but have recovered sufficiently to return to society, and will need to remain on tranquilizing agents almost indefinitely. The family physician, particularly in rural areas, will be called on not only to treat these patients for intercurrent illness but also to supervise the ataractic medication.

A certain percentage of therapeutic failures are due to inadequate dosage. In the absence of satisfactory clinical improvement, signs of effect on the central nervous system such as drowsiness and hypotonia may serve as guides. Curiously, extrapyramidal signs (immobility, rigidity, tremors and drooling), while in themselves annoying, often are associated with improvement. Lowering the dosage or adding antiparkinsonism agents such as benztropine methanesulfonate (COGENTIN®), or both, readily control these symptoms. Incoordination, mental confusion and convulsions are signs of overdosage and call for prompt discontinuation of the medication. After the toxic signs have cleared, a period of clinical improvement may follow; it may then be safe to resume the medication at a lower dosage.

With a number of tranquilizing drugs now available, it is obvious that a change of medication is indicated when annoying or dangerous side reactions occur. Less obvious is what constitutes an adequate trial. Some patients respond more favorably to a second tranquilizer after failing to respond to an adequate trial of the first. Some do not benefit appreciably from any of these agents.

Concluding Comment

The tranquilizing drugs have already become established as valuable therapeutic agents, but it will be some time before we

know how they act, which are best for a particular condition, and how to use them. Since they are not all alike, the physician would do well to familiarize himself with one or more from each of the principal classes rather than to try to know something about all of them. Undoubtedly, many new drugs will appear, some of them different and others very similar to drugs already available.

The tranquilizing agents have definite limitations. They do not help all patients nor are they beneficial in all types of nervous and mental disturbances. When they are effective, they may reduce anxiety to a more normal level but they do not solve life's problems. Except in the most simple cases, additional therapeutic procedures obviously are needed. The older sedatives which promote sleep are still more effective in treatment of acute insomnia and when command sedation is required.

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VARIETY CLUB HEART HOSPITAL, UNIVERSITY OF MINNESOTA

Clinical Applications of Radioisotopes

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ALTHOUGH numerous applications have been found for radioisotopes in the fields of biology and medicine, most of them have been of an investigative nature. In order for a particular application to find its way into clinical medicine, it should (1) be radiologically safe for patient and medical personnel, (2) be superior to pre-existing procedures, and (3) be simple and inexpensive.

Table 1 lists the applications which we have found to satisfy these criteria. These procedures are now in routine clinical use at the University of Minnesota Hospitals and certain other medical institutions in this area.

Various departments of the University Hospitals are constantly probing other uses of radioisotopes. After a reasonable period, these methods are evaluated and then abandoned, continued on an experimental basis, or adopted as routine procedures. The initial enthusiasm for many applications wanes with later experience, and some radioisotope tests which enjoyed considerable popularity a few years ago are now in discard. An example is the employment of diiodofluorescein and radioiodinated serum albumin for external scanning of the skull for brain tumors. This is now known to be only 60 per cent efficient, and preference is given to cerebral angiography and encephalography.

ELMER C. PAULSON

DONN G. MOSSER

Radioiodine (I^{131})

Over the last dozen or more years, radioiodine has received extensive consideration from many quarters as an agent to probe the thy-

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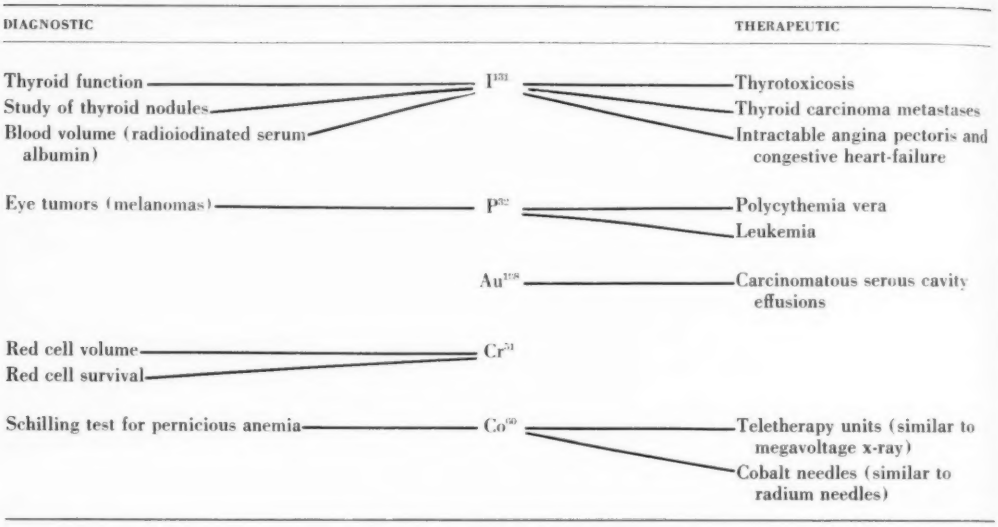
TABLE 1

CLINICAL APPLICATIONS OF RADIOISOTOPES AT UNIVERSITY OF MINNESOTA HOSPITALS



roid gland. Rarely has a single diagnostic procedure enjoyed such interest and multiplicity of applications. In the earliest stages of development of this test, the urinary output of radioiodine after an oral dose was used. Since then, the uptake of radioiodine by the thyroid gland itself, the rate of conversion of inorganic to protein-bound iodine in the blood, the salivary output of iodine, and various methods of fractionating all these studies over a period of time have been described. These investigations have all contributed a tremendous amount of information to our basic knowledge of thyroid function.

We feel that the routine clinical application of the radioiodine thyroid study can be simplified to one easy procedure, namely, the 24 hour thyroid uptake test. We also employ the conversion ratio in selected cases. We prefer to see these tests carefully correlated with the clinical findings rather than to use other time-consuming isotopic procedures. To avoid obvious errors in using the test, we screen all patients in accordance with the outline in table 2. As a guide to the clinical correlation of the test, we find table 3 useful.

The amount of radioiodine used in the tracer dose is worthy of comment. Some years ago, with the earliest type of Geiger-Müller tubes, it was necessary to give 100 to 150 μc. to perform a satisfactory uptake test. At present, employing the more sensitive scintillation tubes, only from 1 to 10 μc. is needed. If the blood plasma proteins are to be studied in various ways, it is necessary to give more than this, usually in the neighborhood of 25 to 50 μc. The earliest attempts at automatic scanning of the thyroid region required very large doses, up to 500 μc. The latest equipment for this purpose is said to perform satisfactorily with as little as 30 to 50 μc. Safety considerations call for the smallest possible tracer dose which will produce satisfactory results, and this constitutes the best argument in favor of a scintillation tube for performing the routine thyroid uptake test.

In the estimation of thyroid function, we consider the normal range of uptake to be between 15 and 45 per cent. An uptake below 10 per cent warrants a definite diagnosis of hypothyroidism. An uptake in the 10 to 15 per cent range suggests such a diagnosis but it is not entirely definite. A thyroid uptake test will pick up only those cases of hypo-

thyroidism characterized by a low avidity for iodine. There is another group of cases of hypothyroidism which have a normal avidity for iodine but lack the ability to convert the iodine into thyroxin. These cases cannot be diagnosed by the thyroid uptake test, and it is important to realize this when results of the uptake test are normal in the face of frank symptoms of hypothyroidism. Unfortunately, none of the other procedures of studying thyroid function with I^{131} are able to detect this particular group. The only way to distinguish them is with chromatographic or electrophoretic analysis of the iodinated serum proteins.

The uptake test is more valuable at the upper end of the scale, in diagnosing hyperthyroidism. Falsely high values will occur in iodine starvation, uremia and rare cases of struma lymphomatosa (Hashimoto's struma). It is particularly valuable in differentiating other diseases characterized by hypermetabolism, such as anxiety neurosis, parkinsonism and pheochromocytoma. The test can be used through all age ranges from early infancy to senility.

TABLE 2

CONTRAINDICATIONS TO USE OF THE THYROID UPTAKE TEST

1. Pregnancy
2. Pyloric obstruction or diarrhea
3. Iodine medication—three weeks
Lugol's solution
Mineral-vitamin preparations
Cough syrups or cough drops
4. Radiographic mediums containing iodine
Urogram and cystogram—two weeks
Bronchogram
Iodized oil mediums—year or more
Iodine-water mediums—two weeks
Cholecystogram—two to three months
Intravenous cholangiogram—two weeks
Spinogram (only when considerable oil is left in spinal canal)—permanent
Salpingogram
Iodized oil—as long as roentgenogram shows residual oil
Iodine-water mediums—two weeks
5. Hormones
Whole thyroid—three weeks
6. Antithyroid medications
Propylthiouracil, TAPAZOLE®, thiocyanate—one week
7. Miscellaneous
BUTAZOLIDIN®, sulfonamide drugs—two to three weeks

TABLE 3

THYROID ABERRATION

1. Function
2. Size, shape, position
3. Inflammation
4. Neoplasia

In the evaluation of nodules in the neck, the counter is equipped with a cone which is placed directly against the nodule to measure its radioiodine concentration. The only diagnosis warranted after this procedure is a statement that the nodule does or does not represent functioning thyroid tissue. If the nodule does not pick up radioiodine, it may represent a degenerated thyroid adenoma, a thyroid carcinoma, or some other type of tissue.

We have found the thyroid uptake test valuable in both diagnosis and management of thyroiditis.[1] Subacute thyroiditis is universally accompanied by a low uptake. This indicates that the patient is either in a hypothyroid status or destined to be in such a status in the near future, and points to therapy with some form of thyroid extract. Since the course of this disease is often more chronic than subacute, the uptake also aids in follow-up, for it rises to normal when the patient has recovered. In struma lymphomatosa, on the other hand, any sort of uptake may exist and a particularly careful correlation with physical and clinical data is important in arriving at the correct diagnosis.

The thyroid uptake of I^{131} is not of value in diagnosis of carcinoma of the thyroid. Although thyroid carcinoma is said to be rare in the presence of hyperthyroidism, we have seen several such cases. In general, the clinical data should be the determining features in deciding whether or not carcinoma may exist in a particular case. A thyroid nodule that picks up less iodine than the surrounding thyroid tissue is regarded with suspicion, but this fact is not as important as the patient's age, the multiplicity of thyroid nodules, and recent change in such nodules.

Therapy of hyperthyroidism with I^{131} rests historically on previous experience with therapy by means of roentgen rays. The principal disadvantage of using roentgen rays for this purpose was the production of skin changes later on, since the skin of the neck is particularly sensitive to radiation. Radioiodine avoids this handicap. Tens of thousands of patients with hyperthyroidism in this country have been treated with radioiodine, and it looks like the ideal form of treatment for the diffuse hyperplastic type of goiter. Valid contraindications to its use are few. The only rigid one in our practice is pregnancy. The next strongest contraindication is childhood or adolescence. Fear of a future carcinogenic effect has led many to limit this procedure to persons over the age of 50 or 40 years. We have not felt constrained by such age limitations, although we tend to discourage its use in younger patients. In such cases we point out that surgical treatment is preferable. If the patient is subject to carcinophobia, he should certainly have the opportunity to reject this form of treatment beforehand rather than suffer mental agony afterward.

In approximately 85 to 90 per cent of cases of diffuse hyperplastic goiter, cure can be achieved with a single dose of radioiodine calculated on the basis of the uptake and the thyroid size. About 5 to 10 per cent of the patients require an additional dose six months to a year later, and another 5 per cent become hypothyroid, although this effect may be only temporary—for 6 to 12 months. Toxic nodular goiter generally should be handled surgically, both to remove the excess nodular thyroid tissue and to relieve any suspicion of carcinoma. In elderly patients, however, radioiodine will successfully relieve the thyrotoxicosis but will not appreciably alter the size of the nodular goiter. In poor operative risks, it is permissible to ignore the possibility of a lurking thyroid carcinoma and employ radioiodine instead of surgical treatment.

The role of radioiodine in management of thyroid cancer has received wide attention, entirely out of proportion to its importance. Only a small proportion of thyroid carcinomas produce iodophilic metastases that can be handled with this modality. After total thyroidectomy, these patients are given tracer doses and subjected to body scanning in conjunction with appropriate radiographic studies. Doses of 80 to 100 μc have produced satisfactory palliation in the patients we have studied.

Our experience with treatment of intractable angina pectoris and congestive heart-failure by induction of myxedema with I^{131} has been very limited. We believe that strict criteria of selection are necessary. In our small series, approximately 50 per cent of the patients were benefited.

Radiophosphorus (P^{32})

Radioactive phosphorus or P^{32}, a pure beta-ray emitter, enters into the metabolism of actively growing tissue and thus lends itself to certain diagnostic as well as therapeutic procedures. Numerous investigations have shown that P^{32} is incorporated into actively growing cancers. However, unless the cancers are located on or near the surface of the body, it is difficult to measure their P^{32} content because of the absorption of the beta rays by a few millimeters of tissue. Nevertheless, with specially adapted Geiger-Müller counters, P^{32} has proved of value in distinguishing melanotic tumors of the eye. This is of particular importance in cases of detached retina in which the ophthalmologist wishes to know whether or not a melanoma lies behind the retinal detachment. Although melanomas absorb P^{32} in greater than background quantities, this is not the case with retinoblastomas, where it is of no value. Dr. Donald Shahon of our institution has followed the lead of Nakayama of Japan in exploring the usefulness of P^{32} in identifying carcinomas of the stomach and esophagus with specially built Geiger-Müller tubes that can be placed directly within these organs. Although fraught with many technical difficulties, these investigations have proved encouraging.

Therapeutically, P^{32} finds its greatest usefulness in treatment of polycythemia vera. The principal reason for treating this disease is to avoid the possibility of thromboses which may occur in the heart or brain as well as in less serious sites. This thrombotic tendency will be

the more marked in those patients who have high platelet counts, and consequently one should pay close attention to these counts. Rarely, patients have been seen who have had platelet counts up in the millions in the face of normal or subnormal red blood cell counts. The hematocrit value also merits attention in these cases, and we prefer to have phlebotomies done until the hematocrit is down to 55 per cent before treating the patients. The main reason for this is that it takes a couple of months before the effects of P^{32} are evident, and phlebotomies will give the patient some relief from symptoms as well as serve as a temporary safeguard against the thrombotic tendency. Some observers have criticized the practice of phlebotomy as serving as a further stimulant to the bone marrow. However, one may also argue that this stimulation provides impetus for more efficient use of the P^{32}. The dosage rate ranges from approximately 3 to 5 mc. and is based entirely on our experience.

Usually, re-treatment is required at intervals of 6 to 12 months, although this time interval is not rigidly followed. It is now quite generally recognized that P^{32} is our most efficient agent for controlling polycythemia vera. The question has been raised whether this form of therapy contributes to the development of leukemia. It is known that there is a natural metamorphosis from polycythemia vera to leukemia, and this is likely to occur after a number of years. It seems most logical that the use of P^{32} spares the patients from fatal cardiac and cerebral thromboses, thereby making possible the subsequent transition to leukemia.

Therapy of leukemia with P^{32} is quite popular in some quarters. We have felt that we can deal with chronic lymphatic and myelocytic leukemias more efficiently with chemotherapy or radiation with roentgen rays. Small doses of roentgen rays, appropriately delivered, with daily blood counts, afford such an accurate guide to the patient's progress that we have not felt inclined toward extensive use of P^{32}. We have used it in a few cases. In one of these, there was no splenic or lymph node enlargement, and consequently we were left with the choice of either spray radiation of large bone fields or employment of P^{32}. However, in our department we maintain that roentgen ray radiation is the therapy of choice when radiation is to be used.

Radiogold (Au^{198})

Colloidal radiogold is both a beta-ray emitter and a gamma-ray emitter, principally the former, and has two therapeutic applications: treatment of carcinomatous effusions in the pleural and peritoneal spaces, and interstitial injection into and around tumor masses.

The rationale of using this agent to treat carcinomatous effusions is its adsorption on serous surfaces and the engulfment of its particles by localized lymphatics, both of which actions are believed to inactivate the carcinomatous metastases at these sites. Unfortunately, many peritoneal carcinomatous effusions are due to the obstruction of the portal circulation by carcinoma rather than to small lesions that are studded on the serous surfaces. Radiogold cannot be expected to benefit this.

In general, radiogold has been disappointing. It is difficult to select suitable candidates for its application, since most of these patients are in the terminal stages of carcinoma. Of those who survive longer than six weeks, approximately half receive some benefit in that the rate of fluid formation is diminished.[2] This is the only benefit claimed for this type of treatment. At present, the only type of case which we feel merits treatment with radiogold is carcinoma of the ovary in which there has been a comparatively "clean" excision of the cancer, with the possibility that a few carcinoma cells are floating around in the peritoneal or pelvic cavity.

Interstitial injection of colloidal radiogold into tumor masses is somewhat analogous to implantation of radon seeds. Flocks and Gillis of the University of Iowa have used this method extensively in treatment of prostatic carcinoma. A. I. Sherman and others at Washington University in St. Louis have injected this material into the broad ligaments as part of the therapeutic schedule for carcinoma of the uterus. At our institution, we are still using radon seeds where tumor implantation seems

indicated, since the dosage distribution can be executed more carefully in this manner. The distribution of colloidal radiogold, once it leaves the injection needle, is determined by the path of least resistance, and this may not always be the ideal arrangement. Another method of using Au^{198} is in the form of gold "grains," which are small fragments of radiogold wire that can be inserted into tumor beds.

Other Radioisotopes in Clinical Use

Radioactive chromium or Cr^{51} in the form of sodium chromate is now the most widely used radioisotope for tagging red blood cells. It is used both in determining the red blood cell volume and for red blood cell survival studies. Hematologists have found the latter application of value in the study of hemolytic anemias. An alternative and more simple method of determining blood volume is the employment of radioiodinated serum albumin in a dilution method. The entire determination can be completed in 20 or 30 minutes.

Radioactive cobalt or Co^{60} finds its principal medical application in the form of the teletherapy unit known as the cobalt bomb. Dr. R. F. Schilling of the University of Wisconsin has devised a very ingenious test for pernicious anemia which actually determines the presence or absence of intrinsic factor in the stomach lining. This is of particular use in patients who have been under treatment with various vitamin preparations and liver extract. In such cases, the blood picture is normal and it would be necessary to wait several months for the characteristic findings and symptoms of pernicious anemia to become manifest. The Schilling test employs a special form of vitamin B_{12} in which the cobalt atom of this vitamin has been rendered radioactive. In pernicious anemia, there is practically no absorption of this substance (vitamin B_{12} Co^{60}) from the gastrointestinal tract. If a capsule of intrinsic factor is ingested with this substance, the amount of absorption increases considerably. The test also can be employed in the diagnosis of sprue, where there is no absorption of vitamin B_{12} Co^{60} either with or without the addition of intrinsic factor, since the absorptive mechanism of the intestinal tract itself is at fault.

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The Chemical Basis of Radiation Damage

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THE ready availability of artificial radioisotopes over the past decade has increased the variety and extent of use of ionizing radiations as diagnostic and therapeutic agents. The introduction of atomic nuclear reactions as a source of energy in warfare and in industry has increased still further the present and potential exposure of humans to radiation injury. These circumstances have markedly increased efforts to uncover the mechanisms of the biologic action of ionizing radiations.

Alpha, beta, gamma and roentgen radiations and neutrons produce similar biologic effects, although their efficiency varies owing to their characteristic dose distribution of energy among different tissues and along individual ion paths. This fact allows roentgen rays, which are readily available and controllable, to be used as a matter of convenience in studies of radiation biology with the assurance that the fundamental tissue responses produced are in general like those resulting from the absorption of the other forms of ionizing radiations. The salient feature of ionizing radiations is that they deliver energy to atoms which effects an alteration of atomic structure by disturbing the position and relations of the planetary electrons to the atomic nucleus. Displacement of these electrons from stable orbits to higher-energy orbits in the atom is known as "excitation." Removal of an external orbital electron gives an ion pair from each atom—the negatively charged ejected electron and the larger positively charged atomic residue. Most attention in radiation biology has been focused on the latter process called "ionization" since the methods of dosimetry of "ionizing radia-

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tions" depend on ion density measurements and because ionization can produce permanent molecular alterations.

Two concepts have been employed to describe the sites of primary radiation effects in tissues. The direct concept[1] postulated that a molecular disruption of specific and sensitive organic molecules occurs by direct excitation and ionization of these molecules. Probably this mechanism becomes relatively more important as the concentration of the solute molecules increases and with the higher radiation doses, and it is exemplified when dry crystals are irradiated. A more recently developed concept is referred to as the indirect action of radiation and describes a process in which the primary event is the ionization of water molecules with the production of highly reactive products.[2-4] These substances, which are mainly oxidants, then effect alterations or inactivations of important solute molecules which are essential to cell growth or metabolism. The latter concept gives recognition to the fact that the major constituent of biologic systems is water, and it can therefore be expected that when ionizing radiations are absorbed in such fluids, the water molecules will be those that are predominantly hit. The indirect concept receives special support from the fact that chemical changes among water molecules can be demonstrated to occur from irradiation with alpha and beta particles and roentgen rays. If the water is oxygenated, as is the case in biologic systems, hydrogen peroxide (H_2O_2), oxygen (O_2) and hydrogen (H_2) gases are produced. From indirect evidence the primary reaction is believed to be the ultimate formation of hydrogen atoms and hydroxyl radicals:

$$H_2O \rightarrow H + OH$$

In the presence of dissolved oxygen the hydrogen atoms combine with oxygen to form O_2H (perhydroxy) radicals:

$$O_2 + H \rightarrow O_2H$$

Hydrogen peroxide is then formed by two reactions:

$$O_2H + H \rightarrow H_2O_2 \text{ and}$$

$$OH + OH \rightarrow H_2O_2$$

The relative amounts of these products formed from water molecules depend on the intensity and dose rate of irradiation and on the kind of radiation employed. For example, hydrogen peroxide is produced in water by alpha particles irrespective of the presence of dissolved oxygen, whereas the other forms of ionizing radiation require for hydrogen peroxide formation the use of oxygenated water. The O_2H and OH radicals and H_2O_2 are oxidizing agents while hydrogen atoms are reducing agents. These substances, according to the concept of indirect mechanism of radiation effect, produce by the reactions of oxidation and reduction alterations in chemical structure of all the sensitive and essential cellular components.

Alteration of substances of great importance to cellular structure and function have been observed to occur from radiation, and some of these are of a nature that could be expected to result from the action of the products of irradiation of water. Reduced diphosphopyridine nucleotide, cytochrome C and sulfhydryl groups are oxidized, some enzymes are inactivated,[5] and the properties of simple proteins[6] and of nucleic acids[7] are altered. While some of these results can be produced in vitro only with radiation doses larger than those which affect intact animals, they nevertheless point out that substances involved in cell function are capable of modification by radiation and indicate that other essential cell constituents, or those already mentioned, as they exist in the cell, may be affected by lower radiation doses. Of special importance in this regard is the demonstration of the marked reduction of turnover of desoxyribose nucleic acid in tumors[8] and liver[9] by radiation doses not too far removed from those which produce obvious biologic effects.

No single effect can be expected to be at the groundwork of all forms of radiation injury, since a cell is a highly organized system of diverse constitution and structure among its parts, and this diversity is still further extended among cells of the different tissues. Thus it is to be expected that the actual end results of radiation overexposure will vary not only because of the complex physical and chemical factors of energy absorption but also with the subtle organization and composition

of the cells. Hematopoietic and germinal tissues are most sensitive to radiation, followed in order, it is generally stated, by intestinal epithelium, skin and connective tissue. It is frequently indicated that muscle and nerve cells are refractory to radiation. These deductions have been mainly derived from observations of destruction or alterations of cell structure as indicated by histologic methods. Our studies have been aimed at the discovery of alterations of chemical composition of tissues produced by radiation and the correlation of these with deranged organ functions. An important over-all result of our work is that we have been able to demonstrate significant changes caused by radiation in composition and function of some tissues which do not exhibit anatomic evidence of radiation injury.

Electrolyte Losses and Muscle Damage

One of the prominent features of radiation sickness is the attendant upset of salt and water metabolism consequent in part on vomiting, diarrhea or diuresis. In our investigations of this result of radiation damage, as in all our work in this field, we have employed mature male rats which were given 700 r of whole body x-radiation. This dosage kills half the animals within a two week period. The results given in table 1 were obtained by comparing the amounts of potassium, sodium and chloride in the food ingested by the animals with the amounts of the same mineral ions in the excreta.[10] It is evident that one of the aspects of radiation damage in the rat is a significant early loss of body potassium and sodium and that there is a negative balance of chloride which, however, does not become evident until the fourth to sixth day after irradiation. Actually our later work[11,12] has shown that the method of metabolic balance for estimating body losses of electrolytes gives, at least in the rat, somewhat spurious results as to the quantities and time relations of losses of inorganic ions from the fluid compartments of the body. This circumstance stems in large part from the fact that the rat does not vomit, and large volumes of fluid containing considerable amounts of chloride as hydrochloric acid accumulate in the stomach and intestine of the irradiated animals over the early postirradiation periods. Since the animals cease to eat during the immediate postirradiation period the chloride appearing in the gastric contents is derived from the fluid compartments of the body.

A more useful delineation of the actual tissue losses of mass and of electrolytes following irradiation can be obtained by direct examination of the changes in weight and electrolyte contents of the individual organs. Table 2 gives our results[13] of the alterations from control values of organ weights in our series of animals whose total weight loss was 13 per cent at six days postirradiation. These results are expressed as a percentage of the organ weights of control animals. The thymus, spleen and intestines, which are generally recognized to be radiosensitive, suffered, as was to be expected, considerable losses in weight. These results also show a new and important

TABLE 1

DIFFERENCE BETWEEN ELECTROLYTE BALANCES OF EXPERIMENTAL AND CONTROL RATS BEFORE AND AFTER TOTAL BODY X-RADIATION (DATA AS MEQ. PER PERIOD)

Before Irradiation (Days)	*K+*	*Na+*	*Cl−*
0- 2	+0.050	+0.180	+0.124
2- 4	−0.093	+0.145	+0.050
4- 6	−0.081	+0.127	+0.014
6- 8	+0.156	+0.031	+0.047
8-10	−0.113	+0.061	+0.168
10-12	+0.162	+0.107	+0.214
12-14	+0.016	+0.196	−0.077
14-16	−0.100	−0.121	−0.007
16-18	−0.136	−0.008	−0.364
Av.	−0.015	+0.080	+0.019
σ	0.116	0.101	0.169
After Irradiation (Days)			
0- 2	−0.567*	−0.245†	+0.066
2- 4	−0.866*	−0.558*	+0.124
4- 6	−0.112	+0.045	−0.424†
6- 8	−0.033	−0.178†	−0.143
8-10	+0.214	+0.312	+0.183

*Significant at 1 per cent level ($P \leq .01$).
†Significant at 5 per cent level ($.01 < P < .05$).

TABLE 2

TISSUE WEIGHTS OF RATS FOLLOWING TOTAL BODY X-RADIATION WITH 700 R (EXPRESSED AS PER CENT OF CONTROL)*

TISSUE	PERIODS AFTER IRRADIATION								
	3 Hours	*12 Hours*	*1 Day*	*2 Days*	*3 Days*	*4 Days*	*6 Days*	*8 Days*	*10 Days*
Muscle	96.7†	94.4†	95.2†	91.3†	88.3†	80.2†	85.3†	85.4†	87.6†
Supportive	99.2	103.1	103.4	113.1†	100.7	113.9†	105.8‡	102.4	106.7‡
Skin	97.0	97.4	101.4	93.8	86.4	91.1	87.7	94.3	98.2
Liver	101.3	95.8	96.4	90.8	97.2	94.7	94.6	96.1	106.5
Lung	110.8	90.2	101.9	99.4	99.4	112.6	97.0	94.7	97.3
Heart	101.5	105.4	104.8	103.0	97.3	98.8	98.8	97.3	106.6
Kidneys	106.2	104.6	99.0	100.9	86.4	92.1	98.5	94.2	103.3
Testes	99.7	115.0	105.6	108.3	103.1	107.3	88.4	90.2	101.5
Spleen	79.6†	64.2†	57.3†	47.5†	37.4†	36.7†	40.9†	43.1†	60.7†
Brain	103.8	101.6	105.7	107.4	99.1	106.8‡	104.0	97.2	102.1
Small intestine	98.0	88.7‡	83.9†	72.6†	90.1	121.0†	111.2‡	86.4‡	105.5
Large intestine	87.4	82.7‡	90.0	86.5‡	105.1	120.6‡	116.0‡	97.5	97.8
Thymus	101.8	86.4	42.2†	11.5†	22.2†	22.9†	23.5†	26.7†	43.4†

*The body weights of the control and irradiated animals were adjusted by subtraction of the weights of the gastrointestinal contents and of body fat because these are variable and undergo large change of weight in the irradiated animals.

†Significant at 1 per cent level ($P \leq .01$).

‡Significant at 5 per cent level ($.05 \geq P > .01$).

fact, namely, that loss of body weight following x-radiation is primarily associated with loss of muscle mass. Besides indicating that muscle is a radiosensitive tissue, these results are also evidence that the effects of radiation damage have a pattern different from those caused by inanition.[12]

An examination of the chemical composition of the tissues also gives results[11] which point out that muscle should be included among the tissues subject to alteration by radiation. The results in table 3 show the losses of potassium, sodium and chloride from selected organs of the irradiated rats. These results demonstrate that the losses in total body contents of these ions are derived from tissues in proportion to their initial potassium and sodium contents rather than in the order of their classic radiosensitivity as deduced from histologic findings. These findings, and those previously mentioned with respect to alterations of organ weights, indicate that a chemical lesion is at the basis of radiation damage and that it is probable that no cell is exempt from this effect.

Shifts in sodium and chloride from the fluid compartments of the tissues to the gastrointestinal tract and the reabsorption of these ions after about six to eight days, when the recovery of function of the gastrointestinal tract has begun, produce some observable alterations in the acid-base values of the plasma. These observations[11] are summarized in table 4 which indicates production of a metabolic alkalosis over the early postirradiation days.

Cardiovascular Effects

The heart is not frequently thought to be radiosensitive, nor are disturbances of its function considered part of the morbid results of radiation overdosage. Prosser[14] and his coworkers and Hartman, Bollinger, Doub and Smith[15] noted incidental disturbances of heart rate and of electrocardiographic tracings in irradiated animals, and Fulton and Sudak[16] found that x-ray doses of 1000 r were required to produce alterations of the electrocardiographic pattern in the guinea pig. These workers considered the cardiac effects so produced to be a secondary result of hyperkalemia due to adrenocortical insufficiency.

Our work on fluid and electrolyte disturbances following whole body irradiation of rats led us to observe several alterations in cardiac

TABLE 3

CHANGES IN ELECTROLYTE CONTENT OF TISSUES OF RATS AS A RESULT OF TOTAL BODY X-RADIATION

ISSUE	CONTROL (MEQ.)	DIFFERENCE FROM CONTROL VALUE FOR EACH OF THE FOLLOWING PERIODS AFTER IRRADIATION						
		12 Hours	*1 Day*	*2 Days*	*4 Days*	*6 Days*	*8 Days*	*10 Days*
Potassium								
Muscle	6.587	−0.798	−0.191	−0.760	−1.676	−1.096	−1.039	−0.971
Skeleton	1.130	−0.066	−0.119	−0.164	−0.197	−0.214	−0.261	−0.227
Skin	2.570	−0.141	−0.047	−0.131	−0.623	−0.010	−0.316	−0.068
Heart	0.051	+0.005	+0.003	+0.002	−0.003	−0.002	−0.005	+0.004
Kidneys	0.138	−0.025	+0.016	+0.008	−0.015	−0.022	−0.015	−0.010
Testes	0.240	+0.018	−0.013	+0.003	+0.016	−0.039	−0.039	−0.016
Brain	0.095	+0.001	+0.008	+0.004	+0.014	+0.006	−0.002	+0.002
Small intestine	0.444	−0.074	−0.077	−0.148	+0.123	+0.046	−0.086	−0.012
Sodium								
Muscle	1.997	−0.083	−0.031	−0.160	−0.375	−0.288	−0.207	−0.103
Skeleton	3.172	+0.006	−0.134	+0.190	+0.246	+0.027	+0.149	+0.069
Skin	2.809	−0.048	+0.204	−0.034	−0.266	−0.235	+0.078	−0.030
Heart	0.032	+0.003	+0.004	+0.004	+0.004	+0.003	+0.004	+0.011
Kidneys	0.115	+0.042	+0.023	−0.006	−0.030	+0.045	+0.026	+0.044
Testes	0.147	+0.023	−0.006	+0.020	+0.006	−0.021	−0.022	−0.006
Brain	0.052	0.000	+0.001	+0.001	+0.003	−0.003	−0.004	−0.004
Small intestine	0.302	−0.010	−0.046	−0.050	+0.058	+0.072	−0.024	−0.213
Chloride								
Muscle	2.205	−0.130	−0.115	−0.256	−0.448	−0.400	−0.399	−0.525
Skeleton	0.765	−0.003	−0.069	+0.049	+0.046	−0.015	+0.008	−0.063
Skin	3.274	−0.049	+0.114	−0.223	−0.260	−0.260	+0.070	+0.102
Heart	0.025	+0.002	+0.002	0.000	+0.002	+0.002	0.000	+0.005
Kidneys	0.107	+0.016	−0.009	−0.001	−0.016	+0.019	+0.007	+0.024
Testes	0.200	+0.016	+0.006	+0.007	0.000	+0.033	−0.038	−0.012
Brain	0.054	+0.002	+0.004	+0.004	+0.009	+0.003	0.000	+0.003
Small intestine	0.263	−0.053	−0.046	−0.053	+0.083	+0.026	−0.042	−0.193

composition and function which, because of their correlation in time with the periods of death of the animals, appear to indicate that a disturbance of heart function is a factor

TABLE 4

COMPOSITION OF BLOOD OF RATS AFTER X-RADIATION

TIME AFTER X-RAY	HEMATOCRIT	PLASMA (PER CENT H_2O)	MILLIMOLS PER LITER OF PLASMA				
			Na+	*K+*	*M++*	*Cl−*	CO_2
Control	43.8	92.41	143.6	4.80	3.20	107.1	26.9
σ	5.6	0.39	3.1	0.59	0.30	2.8	1.8
Three hours	42.3	92.42	143.2	4.88	3.13	107.4	26.8
Twelve hours	43.8	92.69	140.9	4.40	3.19	103.5*	29.6*
One day	43.7	92.46	146.4	4.98	3.12	105.6	28.0
Two days	41.6	92.40	144.1	4.76	2.97	107.4	29.2*
Three days	52.0*	92.68	140.7	4.56	3.32	108.7	25.4
Four days	43.5	93.63†	143.7	4.77	3.06	112.6†	26.8
Six days	37.2*	93.50†	141.2	4.53	3.15	110.5*	23.6*
Eight days	40.5	93.43†	138.2*	5.09	3.18	102.9*	25.8
Ten days	34.0†	92.60	140.0	4.64	3.08	106.6	25.2

*Significant at 5 per cent level ($0.05 \geq P > 0.01$).

†Significant at 1 per cent level ($P \leq 0.01$).

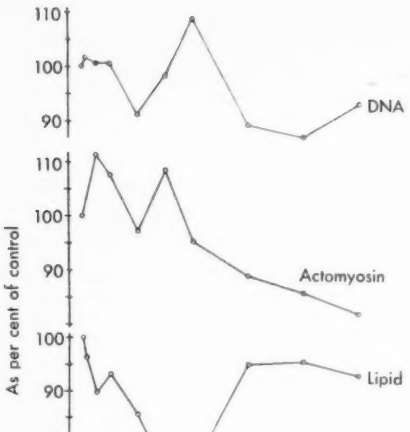

FIGURE 1. Changes in concentration of constituents of the hearts of rats following 700 r total body x-radiation.

causing death from overdosage with x-rays. The chronology of death of the irradiated animals should be kept in mind in considering the time of appearance, or of maximal development, of the abnormalities of heart muscle composition and of cardiac function. At a dosage of 700 r of whole body x-radiation, deaths among the rats begin to occur late on the sixth day and become numerous by the eighth to tenth day; by the fourteenth to fifteenth day, half the animals are dead.

Figure 1 summarizes the changes in concentration of some of the organic constituents of the hearts of the irradiated animals during the first 10 days. The original results[17] were in terms of quantities per kilogram of fat-free tissue. Desoxyribose nucleic acid (DNA) is associated with the chromatin material of the heart and is presumably constant in its weight per nucleus. There are statistically significant decreases of DNA concentration of the heart at two distinct periods following irradiation. One occurs at two days and the other at six to eight days, and these two periods correspond, respectively, with the start of the acute and of the LD_{50} death periods. Since no significant changes occurred in the wet or dry weight of the heart, the changes in concentration of DNA and of the other constituents represent changes in their absolute amounts in the entire heart. Actomyosin is the basic contractile element of muscle. A decrease in its concentration in the heart probably indicates a reduction in work capacity of that organ. Beginning on the fourth day there is a progressive decrease in actomyosin concentration and content which reaches, on the tenth day, a reduction of 20 per cent from the control value. By cardiac lipid is described the total ether-extractable material. The cardiac lipid concentration shows a marked decrease in quantity which coincides in time with the period at which actomyosin begins its progressive decline in amount, but the concentration of lipid returns to near normal over the last four days. In the latter period it appears that nuclear material and actomyosin are replaced on a weight basis with lipid.

As shown in figure 2, there is a transient but statistically significant increase in peripheral venous pressure as measured in the tail vein over the 3 to 12 hour period following irradiation, which is in turn followed by a period of reduced venous pressure. Of special significance is the marked and maintained

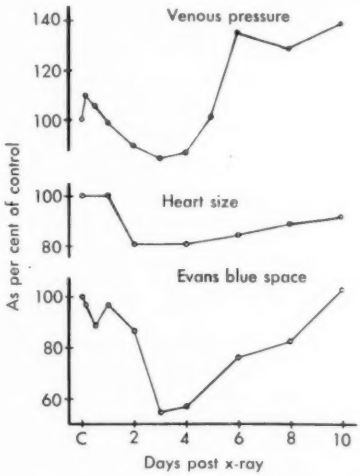

FIGURE 2. Alteration in three cardiac factors of rats produced by 700 r total body x-radiation.

elevation of venous pressure over the sixth to tenth days which is the period of maximum rate of death of the animals. The two lower curves of figure 2 indicate that the period of low venous pressure is correlated in point of time with a reduced heart size, as determined from the area of the heart shadow on the roentgenogram of the chest, and with a reduced Evans blue space (plasma volume) in the entire animal. Since the weight of the heart does not change in the irradiated animals, we interpret the reduction of heart size to be due to a reduced volume of blood contained in the atria and ventricles. Cardiac dilatation is a classic sign of heart-failure, but we have seen most frequently a reduction of heart area which is inconsistent with simple cardiac decompensation. However, in some cases in which we have been able to examine animals a few hours before their death we have seen a considerable enlargement of the heart shadow.

The upper curves of figure 3 indicate significant increases in the amounts of chloride and sodium in the lungs over the last four to six days of the 10 day period. These results can be taken to indicate pulmonary edema. The lower line of figure 3 shows the marked change in plasma volume of the heart muscle itself which is seen over the sixth to tenth days. These data were obtained from the Evans blue content of the bled-out heart. This observation indicates a marked change in dynamics of blood flow through the heart tissue during the terminal period. We have shown previously that large changes in plasma volume of the heart can be induced experimentally by injection of such agents as epinephrine, which have a marked effect on hemodynamics.[18]

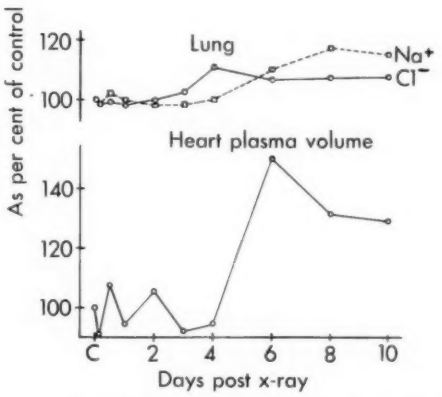

FIGURE 3. Evidence of pulmonary edema and of altered hemodynamics in rats given 700 r total body x-radiation.

We could not make absolute measurements of heart sound amplitude, and our results were recorded as the ratio of the amplitude of the first sound to the second sound. These observations showed a marked relative increase of the first heart sound. Since the first heart sound is related to mitral valve action we take this observation to indicate some alteration in the mechanical events in the heart.

Two types of cardiac arrhythmia have been detected from the electrocardiograms. The first type is correlated with the respiratory cycle, that is, every fifth to sixth heart beat there is short P to P interval and a low R wave. In the second type of arrhythmia there are alternate groups of three to eight beats—each group having its own R to R and P to P distance and R height. There are also some changes in the start of the T wave of the electrocardiograms of the irradiated animals but space does not allow a full discussion of the electrocardiographic data.

The first type of cardiac arrhythmia is most frequently seen during the second to sixth days post irradiation, while the second type is characteristic of the 8 to 10 day period. These changes in cardiac function can also be described by noting the irregularity of the measured R heights and of R to R distances. Figure 4 shows a 350 per cent increase in the standard deviation of the R heights which is attained by the eighth day and the changes of mean R height over the postirradiation period. The changes of mean R to R interval are also shown as variations of the heart rate as beats per minute.

In summary, our data show marked changes in the organic composition and fluid balance of the heart; an increase of venous pressure; a tendency toward pulmonary edema; a series of electrocardiographic alterations and evidence of altered mechanical activity in the heart, all resulting from an LD_{50} dose of

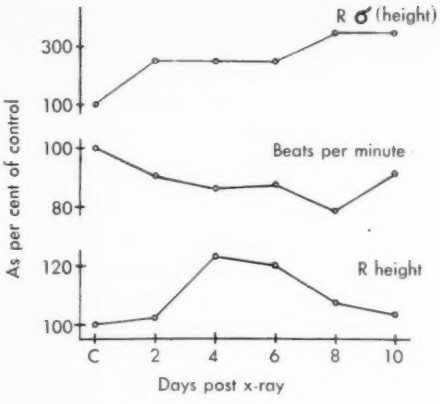

FIGURE 4. Observations derived from electrocardiograms of rats given 700 r total body x-radiation.

x-rays. Since all the alterations of composition and function occur during the LD_{50} death period, some form of heart-failure may be a factor in determining death during this period. An important question in regard to the cardiovascular effects of radiation overexposure is whether or not the effects are due to direct radiation damage of the heart, since they conceivably might be a secondary result of damage to other organs. Work now in progress has indicated that electrocardiographic abnormalities can be produced by x-radiation of the chest alone.

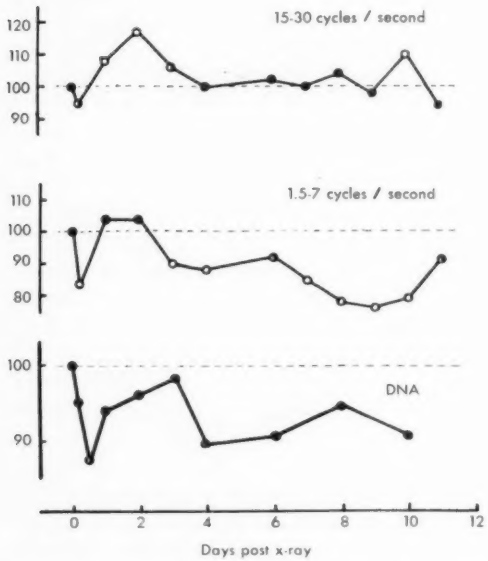

FIGURE 5. Correlation of brain desoxyribose nucleic acid content and of electrocorticographic patterns in rats following 700 r total body x-radiation.

Effects on the Central Nervous System

The central nervous system is generally regarded to be highly resistant to the effects of ionizing radiation. This conclusion is based on the observation that in order for total body irradiation to produce detectable changes in brain structure, grossly supralethal doses (>1000 r) must be given.[19] There are, however, reports of alterations of central nervous system function with substantially lower doses of radiation than those required to produce structural damage in brain tissue.[20,21] Our observations[11] of changes in the chemical composition of tissues of irradiated animals gave results which suggested that the brain may contain a small population of highly radiosensitive cells. Accordingly an examination was made of the associated changes of brain composition and of electrocorticographic patterns in rats given 700 r acute whole body x-radiation.[22]

Significant fluctuations in water, sodium and chloride contents of the brain were observed at one, three, four and six days post irradiation, and the alterations from the normal in desoxyribose nucleic acid (DNA) are shown in figure 5. As is also shown in the same figure, alterations of bio-electric phenomena of the brain were observed which appear to be associated in time with the fluctuations of DNA content of the same organ. The slow (1.5 to 7 cycles per second) and fast (15 to 30 cycles per second) electrocorticographic rhythms were expressed as a percentage of the alpha (8 to 12 cycles per second), since the alpha rhythm was constant among the animals and provided a stable basis of comparison.[22] These results are shown in figure 5 as a percentage of the preirradiation control values.

These experiments have demonstrated a significant decrease in DNA and significant depressions of both the high and low electrocor-

tico; raphic frequencies (related to the alpha activ .ty) in the first 3 to 12 hours following irrad iation. This period is followed by a two to th ee day period in which the brain DNA and the low-frequency activity return to normal levels. Finally there is a period during which the high-frequency activity becomes normal but low-frequency activity and the brain DNA content are depressed. Periods of alterations of depression and enhancement in conditioned reflex response of animals receiving 100 to 500 r of localized x-radiation have been reported[23] which resemble in time of occurrence these fluctuations in brain composition and bio-electric activity.

Summary

Evidence is presented demonstrating that the composition of muscle and the composition and function of the heart and brain are affected by ionizing radiation given as x-rays in amounts which do not produce histologic evidence of injury in these organs. The point is made that radiation damage has at its basis a chemical lesion which probably affects the composition and function of all cells and that this lesion is produced by radiation doses which are lower than those causing anatomic damage.

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Sarcoidosis

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SARCOIDOSIS is characterized by the formation of epithelioid cell granulomas which occur with more or less regularity in selected tissues. The symptomatology depends on the tissues involved and on the extent of the infiltrate; apparently there are no toxic products. Thus the disease may be evaluated on an anatomic basis. Occasionally the lesions invade an important organ to such an extent that function is disturbed.

The disease is predominantly a chronic one and may persist for years without causing either discomfort or anxiety. Only a small percentage of persons affected succumb to the disease, and death is attributed to the extensive involvement of a vital organ or to secondary effects on the vital functions of other tissues closely related to the diseased organ. For example, extensive infiltration of the lung may cause collapse of the right ventricle.

Sarcoidosis has been known for about 65 years, but unity of isolated observations was established slowly because the only link connecting the diverse manifestations of the disease was the uniformity of the histologic findings. The present-day concept was formed on this basis alone, but it was soon learned that a variety of agents could produce a sarcoidal reaction and thus its specificity was in doubt. Therefore, especially in dermatology, lesions were interpreted and separated on a morphologic basis.

Boeck described multiple miliary sarcoid and included under this term papular and nodular lesions as well as plaques. Besnier observed a more diffuse type of lesion which he called lupus pernio. Brocq and Pautrier called similar lesions angiolupoids, and Darier, with Roussy, discovered subcutaneous nodules which were to be known as Darier-Roussy sarcoid. Later, an erythrodermic or diffuse scaling eruption was aligned with sarcoid by Pautrier. Although all these lesions were identical histologically, neither their discoverers nor dermatologists in general would accept a single, inclusive term to designate them.

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Presented before the American Academy of Dermatology and Syphilology at Chicago.

The early literature on sarcoid was largely in the domain of dermatology and was mostly descriptive. Later, reports appeared which were initiated because of detached localizations of lesions. Thus dermatologists, oculists, internists, pathologists and others became concerned with lesions which when examined microscopically showed sarcoidal structure. This naturally led to an effort to explain the pathology and pathogenesis.

Epithelioid tubercles had long been known as a type of tuberculous manifestation. Therefore, tuberculosis was immediately associated with sarcoidosis. However, even though the similarity to tuberculosis was striking, dissimilarities were more so. The lack of positive bacillary findings, the negative results of animal inoculations, the frequently negative tuberculin reactions, and the benign and torpid course could not be correlated readily with a tuberculous infection. Nonetheless, tuberculosis in some form or other had an appeal which could not or has not been eliminated in considering the possible causes of sarcoid.

Evolution of knowledge about sarcoidosis was largely a matter of correlating isolated reports, by which the percentage of involvement of certain tissues could be approximated. It was found that the hilar nodes, lungs, bones, skin or eyes, for example, often were invaded regardless of the presenting lesion, and that the extent of the process could be ascertained only by examining frequently involved structures. Gradually it became apparent that involvement of a single organ was not the rule and that sooner or later one could expect that other selected tissues would participate.

It is unnecessary to review the work of Schaumann, Leitner and others or to stress the rarer syndromes, such as uveoparotitis. We are more concerned here with the importance of sarcoidosis in diagnosis today. The trend of the literature points to the fields where it is a problem. Earlier, emphasis was on identification of odd lesions with sarcoidosis, while the present literature concerns confirmatory investigations that may assist in resolving controversial findings.

The percentage of error in diagnosing skin lesions as sarcoid has been small because of the clinical and microscopic evidence, but when other organs have been in question the diagnosis often has been missed. Thoracologists of long experience now diagnose as sarcoidosis many cases which they formerly believed were something else. It is particularly in the field of chest diseases that a knowledge of sarcoidosis is important, owing to the high incidence of involvement of the hilus and lung. In fact, one may say that such involvement is what makes sarcoidosis an important disease. However, a knowledge of sarcoidosis as a disseminated disease is essential regardless of one's particular field of interest, and all of us should be aware of efforts that are being made to improve its diagnosis.

Little can be added to the morphologic descriptions or to the roentgenographic examinations of the chest and examinations of the eye. Routine laboratory tests have given some information but none are absolute. Tuberculin sensitivity has been stressed, but no one will rule out sarcoidosis in the face of a positive test. The Kveim test is not standardized; a commercial antigen is not available and its position has not been firmly established.

Information concerning the histology of the epithelioid granuloma has increased greatly, and it has been emphasized that it is no longer permissible to diagnose sarcoidosis from a microscopic section alone. Bacteria, spirochetes, fungi, foreign substances and possibly a specific factor may produce sarcoidal reactions. Experienced histologists are able to differentiate the various sarcoidal reactions to some extent, at least, but wisely ask for all the information possible before making their decision. Thus, sarcoidosis may be diagnosed from a microscopic section only with the utmost caution.

When sarcoid was considered an isolated lesion, examinations were, of course, limited. After it became recognized as a systemic disease, all manner of diagnostic procedures were applied in cases in which its presence was suspected. Recently, biopsy of muscle has been included, but one would hardly recommend such a procedure as routine.

The effects of pregnancy on sarcoidosis have been studied, with the conclusion that

pregnancy does not affect its course. This was used as an argument against a tuberculous etiology. Since sarcoidosis is such a static disease, or at least a slowly evolving one, we would not expect much influence by pregnancy. Nevertheless, endocrine factors, broadly, must play a role, because the steroids do affect the lesions.

Careful dissection and excision of the prescalene gland afford another tissue for microscopic examination, and when there is other evidence of sarcoidosis the procedure has confirmatory value. It is not difficult to accomplish, but it must be done with all precaution by a surgeon as a hospital procedure. Unfortunately, statistics are not available for comparison, and therefore sarcoidal structure in a lymph gland may not necessarily be acceptable as a diagnostic criterion. The node near the scalene muscle is part of the retrograde drainage system of the hilus of the lung and hence is a readily accessible tissue that may reveal significant pathologic changes, especially in the right hilus. The right hilus itself, of course, can be explored only by chest surgery. Reports on lymph node involvement in sarcoidosis are scarce.

Somewhat related to the lymphatic system is the change in the blood serum. Reversal of the albumin-globulin ratio is noted often enough to be of some value, but only corroboratively, as it occurs also in other diseases.

As already stated, intrathoracic involvement is the most important feature of sarcoidosis, not so much because of symptoms as because of the problem it presents when roentgenographic examination discloses changes which suggest sarcoidosis but must be differentiated from tuberculosis, fungous disease and cancer. A great deal of information has accumulated about intrathoracic sarcoid. Earlier studies described lesions similar to chronic miliary tuberculosis. Gradually many forms of mediastinal and lung changes in various combinations were identified, so that now we know that there is no "typical" picture. Recently, bronchial involvement culminating in stenosis has been observed in severe cases, and biopsy material obtained by bronchoscopy has been very useful in diagnosis. This is in keeping with previous knowledge concerning lesions of the mucous membrane in the nasal cavity, where specific mucosal lesions had been identified. We must, then, be aware of mucous membrane infiltrates which are comparable to skin lesions. Such lesions have also been found in the small intestine, and some cases of ileitis are due to sarcoidosis. Isolated hypersplenism also may be sarcoidal.

TABLE 1

CONCEPT OF SARCOIDOSIS*

HISTOLOGY

A productive epithelioid cell granuloma which does not cause an exudative reaction and does not continue to caseous necrosis

CLINICAL FEATURES

1. Course
   a. Acute or subacute
   b. Chronic
2. No signs of toxemia
   a. No pain
   b. General health good
3. No signs of inflammatory or exudative reaction
   a. Fever rare
   b. No change in sedimentation rate
   c. No collection of fluid in chest
4. Organ localization and manifestations

IMMUNOBIOLOGIC FEATURES

1. No bacillary findings
2. Tuberculin sensitivity low
3. Reversal of albumin-globulin ratio
4. Kveim test
5. Eosinophilia

*From Wurm.

The question of pathogenesis of intrathoracic sarcoidosis has been carefully studied, especially by Hartweg and Wurm. There seems to be proof, based on a large number of observations, that the hilar nodes are involved before the parenchyma of the lung, and involvement of the lung without hilar enlargement is indeed rare. The course of events is fairly uniform even though the changes in the lung may differ quite markedly. Thus, for convenience, stages of development have been defined. Stage I is the onset in the hilus, stage II the pulmonary extension, and stage III the regression and fibrotic period. These stages are in accord with those observed in skin lesions, where one sees onset, extension, a stationary period, and finally regression with or

without slight scarring and telangiectatic atrophy.

A form of sarcoidosis that has startled observers is that in which signs of nephritis first direct attention to the disease. The atypical development and progress and the finding on general examination of other lesions pointing to sarcoidosis led to biopsy of the kidney, which helped establish the diagnosis. Thus, biopsy of the kidney may be added to biopsy of the liver as a possible resort in cases where the procedure is warranted.

Although sarcoidosis is pre-eminently an insidious and chronic process, more acute forms have been observed. Uveoparotitis of the Heerfordt syndrome is one such type. A second, not so well known, is the form ushered in by an attack of erythema nodosum which, instead of subsiding, remains active or recurs promptly after receding. The erythema nodosum lesions are nonspecific, but I have observed one case in which the pathologic features of erythema nodosum changed gradually to those of subcutaneous or hypodermic sarcoid. Subsequent development of sarcoidosis has been observed in many cases of erythema nodosum, so that sarcoid may in some way be connected with an attack of erythema nodosum.

The entire subject of sarcoid is complex. The possibility of wide extent demands extensive examination, but fortunately the percentage of involvement of certain tissues allows an orderly approach, and since the disease selectively seeks certain tissues the specificity of the process seems to be established.

One must keep in mind a concept of the disease such as that given in table 1.

The diagnosis of sarcoidosis is almost always a matter of assembling facts, but histologic examination is much to be desired, and that, of course, depends on visible or accessible suspected tissue. If skin lesions are present, biopsy is readily accomplished. If not, a lymph node or the prescalene pod often is a possibility. Biopsy of liver, kidney and muscle and examination of sternal marrow are additional possibilities.

Clinical, microscopic and roentgenologic findings are the triad on which most diagnoses of sarcoidosis are made.

Therapy of sarcoidosis has advanced with the advent of the hormonal drugs, but corticosteroids must be administered only when there are certain clear-cut indications. One must not give them just to cause disappearance of a lesion. Their use is indicated when a functional or systemic disturbance endangers the patient's welfare, and then they are palliative and not curative. By and large, sarcoidosis tends to regress spontaneously. In my opinion, use of antituberculosis drugs is a mistake unless one is convinced that the condition has a tuberculous etiology. Further, the antituberculosis drugs have not been successful except possibly where tuberculosis and sarcoidosis have coexisted.

The outstanding problem in sarcoidosis is to find the cause or to explain the course of events if it is determined that tuberculosis is the cause.

Discography

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THE incidence of clinically significant disease of the intervertebral disks in the lumbar area is extremely high. In spite of the large number of patients being treated for these ailments, the anatomy, pathology, pathogenesis and optimal treatment are still obscure. This is due largely to the inherent difficulty of studying this area in the living patient. Roentgenographic studies in the form of plain films of the spine and myelograms have played an important part in clinical management of diseases of the lumbar intervertebral disks, but they do not actually portray the internal anatomy and pathology of the disks. It is hoped that discography will add significantly to the basic knowledge of diseases of the intervertebral disks and also aid in clinical management.

HAROLD O. PETERSON

Lindblom[1] in 1948 first introduced discography for clinical use. The technic had been developed on cadavers, and the injected disks had been carefully dissected. This formed the foundation for interpretation of the roentgenographic findings. Experiments were made on animals to determine the damage, if any, resulting from the procedure. Besides the work on animals, Lindblom performed discography on approximately 75 patients. He concluded that it was a valuable procedure and not harmful.

In 1950, Lindblom[2] toured the United States, lecturing and demonstrating the technic. Our experience with discography began in November 1950, immediately after his visit to Minnesota. Since then we have used the procedure in 195 cases, injecting a total of 382 disks. This is an average of about 30 cases a year, compared with approximately 210 myelograms made per year during the same period.

Technic

We have altered Lindblom's technic of discography slightly, primarily in the direction of simplification. The entire procedure is done with the patient prone on the fluoroscopic

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table. In cases in which the lumbosacral angle makes it difficult to visualize the L5 disk space, there is some advantage in flexing the spine by means of a support under the abdomen.

Fluoroscopically, points are located on the back where it will be possible to insert a 20 gauge needle 3½ in. long between the spines, with the tip of the needle directly over the disk when it reaches the subarachnoid space. These points on the back, usually in the midline, are marked with a liquid-lead pencil. After insertion of the 20 gauge needle, a 25 gauge needle 5 in. long is inserted through its lumen directly into the center of the intervertebral disk. The depth of the 20 gauge needle is correct when spinal fluid is obtained and its midline position from side to side can be determined fluoroscopically. Depth of the 25 gauge needle is predetermined, since it can protrude only about 3 cm. beyond the 20 gauge needle. Fifty per cent HYPAQUE® is injected through the 25 gauge needle into the center of the disk. The average amount of medium injected is about 1.5 cc. per disk, with a usual range of 0.5 to 3 cc. (minimum 0.1 cc., maximum 5 cc.). Immediately after the injection, films are made in anteroposterior, lateral and oblique projections.

Interpretation

Interpretation of discograms depends on two entirely different aspects of the examination, the response of the patient to the injection and the appearance of the films.

Pain response—To achieve reasonable accuracy in interpreting the discograms, it is essential to evaluate them in light of the patient's response to the injection. In a typical clear-cut case of herniated intervertebral disk, the patient will experience severe pain, to the point of being almost unbearable, as the offending disk is injected. Distribution of this pain will follow the patient's usual symptomatic pattern but usually is much more severe. Unfortunately, not all patients respond in a clear-cut fashion, and often it is difficult to evaluate the reaction. In atypical instances the pain may be very mild, referred to the wrong area, or exaggerated to the extent that accurate evaluation is impossible.

At present, we believe that if injection of the contrast medium does not produce pain the disk under examination is not significant clinically even though it may be abnormal anatomically. Absence of pain on injection of a disk which is anatomically normal definitely excludes the disk as the source of back or leg pain, past or present.

Appearance of the films—In a normal discogram, a characteristic collection of contrast medium appears in two distinct disklike layers in the center of the intervertebral disk (figure 1). The two layers resemble coins on edge, one below the other, separated by a space containing contrast medium of much less density. This is the appearance of the normal nucleus pulposus, without extension of contrast medium into the annulus fibrosus. Approximately 0.1 to 0.5 cc. is required to fill the normal nucleus pulposus, but there are stages of early disk degeneration when the nucleus is larger and will hold more medium, and still be clinically normal.

As an intervertebral disk deteriorates, the nucleus pulposus becomes dehydrated, and

FIGURE 1. Normal discogram. Nucleus pulposus distended with 1 cc. Hypaque. Annulus fibrosus intact.

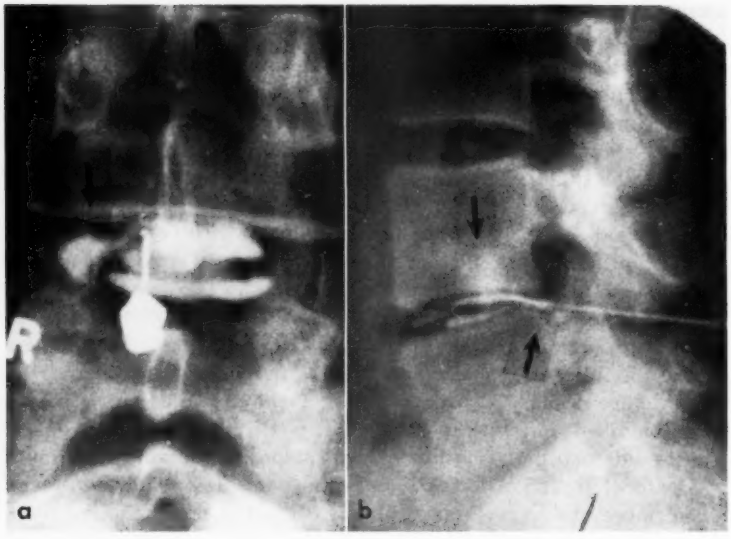

FIGURE 2a. Arrow indicates beginning deterioration of annulus fibrosus on right side. Rest of nucleus pulposus practically normal.

b. Fissure through annulus fibrosus posteriorly, with bulging of posterior ligament into spinal canal. Hypaque is absorbed into body of vertebra (upper arrow).

fragments, tears and fissures are seen in the annulus fibrosus. These can develop in any direction and are demonstrable by discography, since the medium injected into the nucleus pulposus extravasates into these abnormal spaces (figure 2).

If a fissure extends posteriorly through most of the annulus fibrosus, a bulging of the posterior longitudinal ligament into the spinal canal can be demonstrated (figure 3). Similar extensions laterally or anteriorly also can be recognized (figure 4). If the entire disk degenerates, the contrast medium will diffuse throughout the entire disk area (figure 5).

If a Schmorl nodule is present, a "tongue" of contrast medium will protrude directly into the vertebral body at the site of the nodule (figure 6). Occasionally one sees a small piece of bone separated from the anterior superior corner of a vertebral body on plain films of the spine. On discograms, the medium will extend between this small fragment and the vertebra, and this finding has given rise to the opinion that it represents an intracorporal herniation of the disk, occurring probably early in life (figure 7).

Not infrequently, there is a complete break through the annulus fibrosus and posterior longitudinal ligament, and the contrast medi-

FIGURE 3. Degeneration of annuli of two intervertebral disks and fissures posteriorly, but rest of nuclei retain normal appearance.

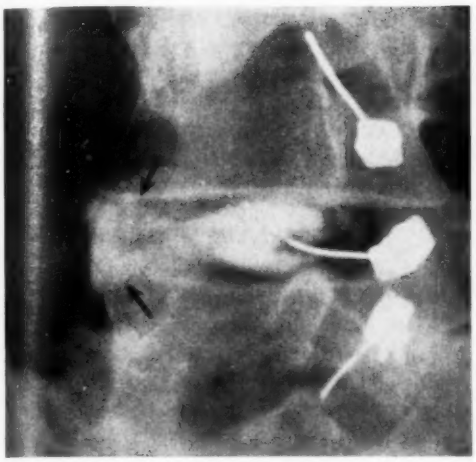

FIGURE 4. Lateral fissures (arrows) and degeneration of annulus, but normal-appearing nucleus on opposite side.

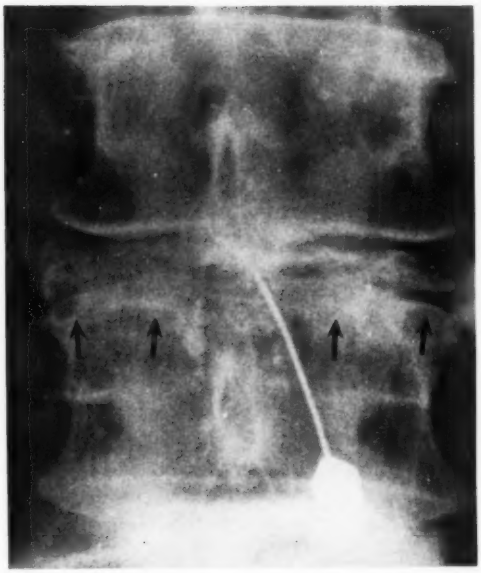

FIGURE 5. Extreme degeneration of entire intervertebral disk.

um then will extravasate freely into the extradural space (figure 7). While this is easily recognized anatomically, the pain response often is minimized, since pressure cannot develop in the intervertebral disk.

Finally, the medium can be absorbed directly into the vertebral body if the needle is in close contact with the vertebrae or if the cartilaginous plate protecting the vertebral body is badly degenerated, thus allowing direct contact between medium and bone (figure 8).

Advantages of Discography

1. Discography is a roentgenographic method for diagnosis of herniation of an intervertebral disk which can replace or supplement myelography in the study of the lower lumbar area. It has its greatest clinical value when the results of myelography are negative or equivocal. A clear-cut normal discogram would appear to be good evidence that the patient does not have symptoms from that disk; the same statement cannot be made for a normal myelogram.

2. There is nothing to aspirate, and since medium is not placed in the subarachnoid space the possible sequelae of residual medium in this area are avoided.

3. This examination helps to develop a

FIGURE 6. Schmorl nodule produced by herniation of nucleus pulposus into vertebral body (arrow).

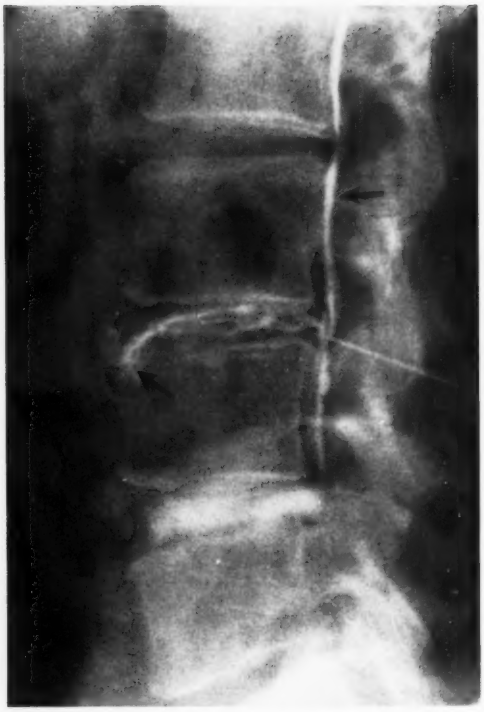

FIGURE 7. Marked degeneration of entire disk. Large amount of DIODRAST® in extradural space (upper arrow), indicating a hole through annulus fibrosus and posterior longitudinal ligament. Intracorporal herniation of nucleus pulposus anteriorly (lower arrow).

more complete concept of the anatomy and pathology of intervertebral disks. It is also hoped that refinements in the procedure and the employment of special technics in more cases will lead to a better understanding of the mechanism of back pain and root pain. For example, we have observed that filling of a Schmorl nodule with contrast medium usually produces back pain. Also, the distention of some disks with contrast medium causes only back pain, without leg pain. This same back pain may be the patient's only complaint, and surgical treatment may relieve it. We have also found that injection of procaine into an offending disk can relieve the acute pain completely, both in the back and in the leg. Long-term relief of symptoms also has been reported after injection of hydrocortisone into the disk.[3] A combination of myelography and discography may enable one to decide which case may be suitable for a more permanent type of injection into the disk—plastics or other substances designed to replace the degenerated disk.[4] Of course, these procedures await further development.

Disadvantages of Discography

1. The major disadvantage of discography is that it is difficult and painful.

2. Its exact value from the standpoint of accuracy of diagnosis has not been clearly established. I personally believe it may have great merit in certain cases, but there remain a number of cases where the diagnosis still is in doubt. Merely performing discography does not mean that a conclusive diagnosis will follow. There are many instances in which abnormal discograms are obtained, but the pain is referred to the wrong leg or to another part of the spine, or is felt in the back only and

FIGURE 8. Marked degeneration of disk with absorption into bone (arrow), indicating deficiency in protective cartilage plate on inferior surface of vertebra.

not the leg, or atypical pain is produced which does not resemble the usual symptoms. Such cases cannot be catalogued as positive or negative.

3. There may be considerable difficulty in interpreting the discograms. Since all intervertebral disks are subject to degeneration of varying degree, a completely normal discogram of an older person is rare. Consequently the combination of an abnormal discogram plus some kind of pain response is relatively common, although neither may be diagnostically significant.

4. Very rarely, discography induces a typical pain response in the face of an apparently normal discogram. An explanation has not been developed for this, and most likely it is not an abnormal disk.

5. A further objection to discography, as contrasted with myelography, is that it is definitely limited to the disks injected; the subarachnoid space cannot be examined. Usually, only the lower three lumbar levels are studied, although there have been reports of thoracic and cervical discography.

6. A final objection to the procedure is cited by those who believe that damage may result from simply introducing a needle into an otherwise asymptomatic intervertebral disk, with or without adding contrast medium. A few isolated cases of aseptic necrosis or infection have been reported.[5] We have not observed this complication and believe it must be quite rare and probably due to faulty technic. Lindblom, from his studies, felt that mechanical damage to the disk from puncture with such a small needle did not occur.

Summary

Discography is a relatively new procedure which gives promise of real diagnostic value in certain selected cases of disease of the intervertebral disks. The procedure may be indicated in cases in which one suspects that disease of the disks is present and myelography gives negative or atypical findings. If combined evidence is insufficient to warrant surgical intervention and the possibility of disk disease persists, discograms may prove decisive. A definitely normal discogram with no pain response to the procedure excludes that disk as the cause of clinical symptoms. A conclusively positive or negative diagnosis cannot always be obtained by discography. It is a relatively difficult diagnostic procedure to perform, and therefore it probably will not become widely employed.

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Fundamentals of the Scoliosis Problem for the General Practitioner

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THE story of lateral curvature of the spine is as old as medical history itself. Hippocrates and his contemporaries described the deformity and wrote of aggressive attempts at its correction. Andry, who coined the word *orthopaedia* in 1741, wrote extensively of scoliosis. The attitude among orthopedic surgeons during the past half-century has ranged from enthusiasm for vigorous treatment to lethargic indifference. Many orthopedic surgeons understand but little concerning the basic principles which lead to successful treatment of lateral curvature. It is small wonder that the general practitioner finds it difficult to counsel his scoliotic patients properly.

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Mechanics of Scoliosis

The spine, in its upright position, normally has a series of balancing curves when viewed from the side. These are physiologic curves and give resilience to the spine. The vertebral column is normally straight when viewed from the front or back; hence scoliosis is an abnormal condition.

In the presence of a lateral curvature, the force of gravity acting on the upright spine causes it to bend with a greater angulation than is found when body weight is eliminated in the supine or prone position. This is true so long as the spine is flexible; but the more rigid a curve becomes, the less difference there will be between the upright and supine curve angulations. Most lateral curvatures do remain flexible to a varying degree, especially during spinal growth. For proper evaluation of the curve angle, an upright x-ray is essential.

If an individual stands with weight equally borne on two legs of unequal length, the pelvis

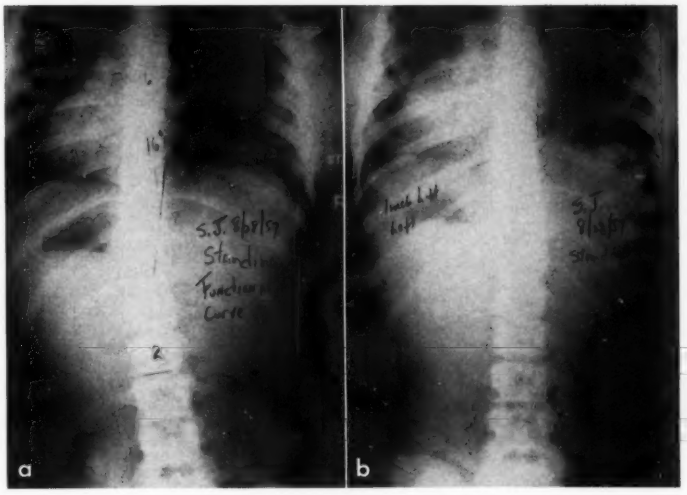


FIGURE 1a and b. Functional curvature of the spine in an 11 year old girl. The left leg is minimally short but a full inch of lift on the left shoe is required to straighten the spine fully. There is no evidence at this time of any structural element in the curve.

will drop on the short side and the spine will bend convexly toward the same side. When the short leg is elevated, the pelvis will become level and the spine will straighten, because it is flexible. For the same reason, it will also straighten when the individual lies down and it will bend to the opposite direction if the shoe elevation is sufficiently raised. If other deforming factors are not present, structural changes of a permanent nature will not occur and the spine will retain its normal flexibility. Such a curve is termed a functional scoliosis (figure 1).

A lateral curvature which persists in all body positions and which the individual cannot correct by any voluntary means is known as a structural scoliosis. Such a persisting curve is always accompanied by rotation of the vertebral bodies because of the eccentric position of the intervertebral joints in relation to the central axis of the vertebral column. Persisting deformities lead to permanent

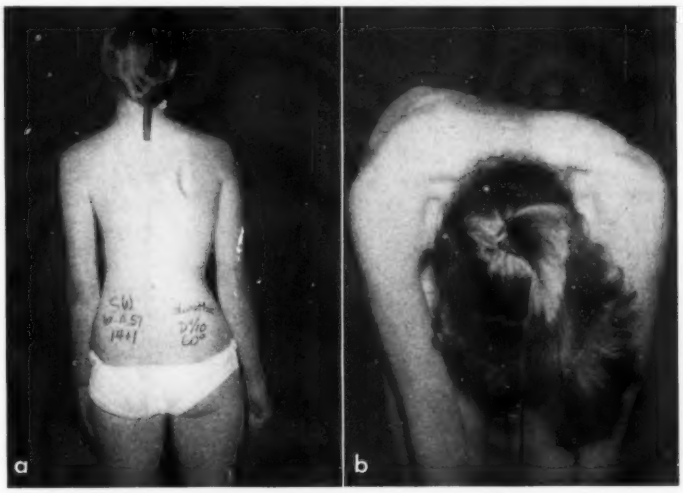
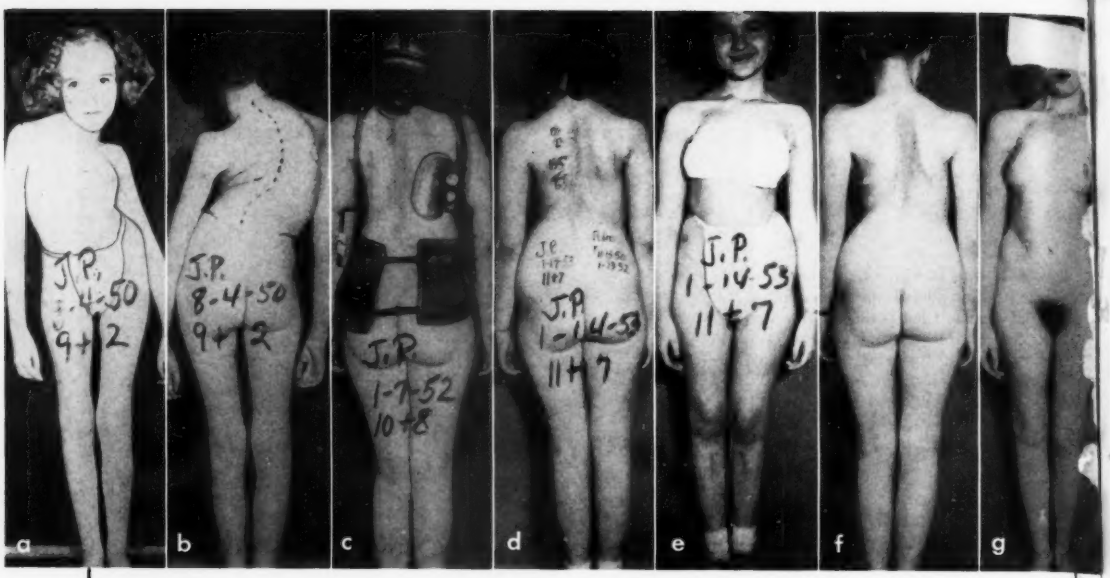


FIGURE 2a and b. Idiopathic curve of the spine in a girl 14 years and one month of age. The curve is 60 degrees and is more visible clinically than the photograph indicates. The rotation on forward bending is clearly shown.



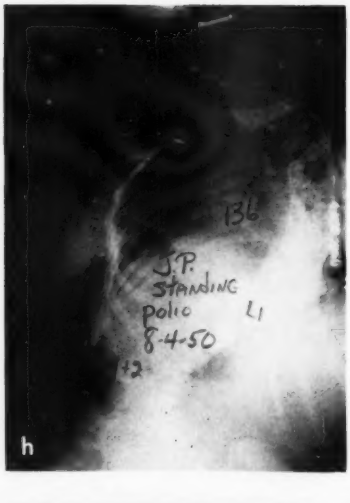


FIGURE 3. Severe postpoliomyelitic scoliosis. Patient first seen for treatment in 1950. Correction was carried out in a Milwaukee brace. Fusion was performed on November 15, 1950 (D1 to L3 vertebrae).

a and b. Preoperative appearance.

c. Standing in Milwaukee brace 14 months after fusion.

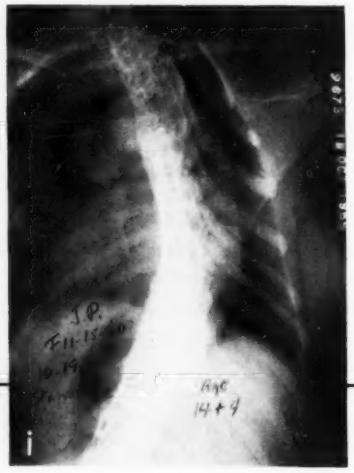
d and e. Good correction maintained without external support 26 months after fusion.

f and g. Same correction maintained in 1957, seven years after fusion.

h. Precorrection x-ray showing 136 degree standing curve.

i. Maximal preoperative correction to 55 degrees in Milwaukee brace, supine.

j. The final correction was at 65 degrees. There has been no change since 1955.



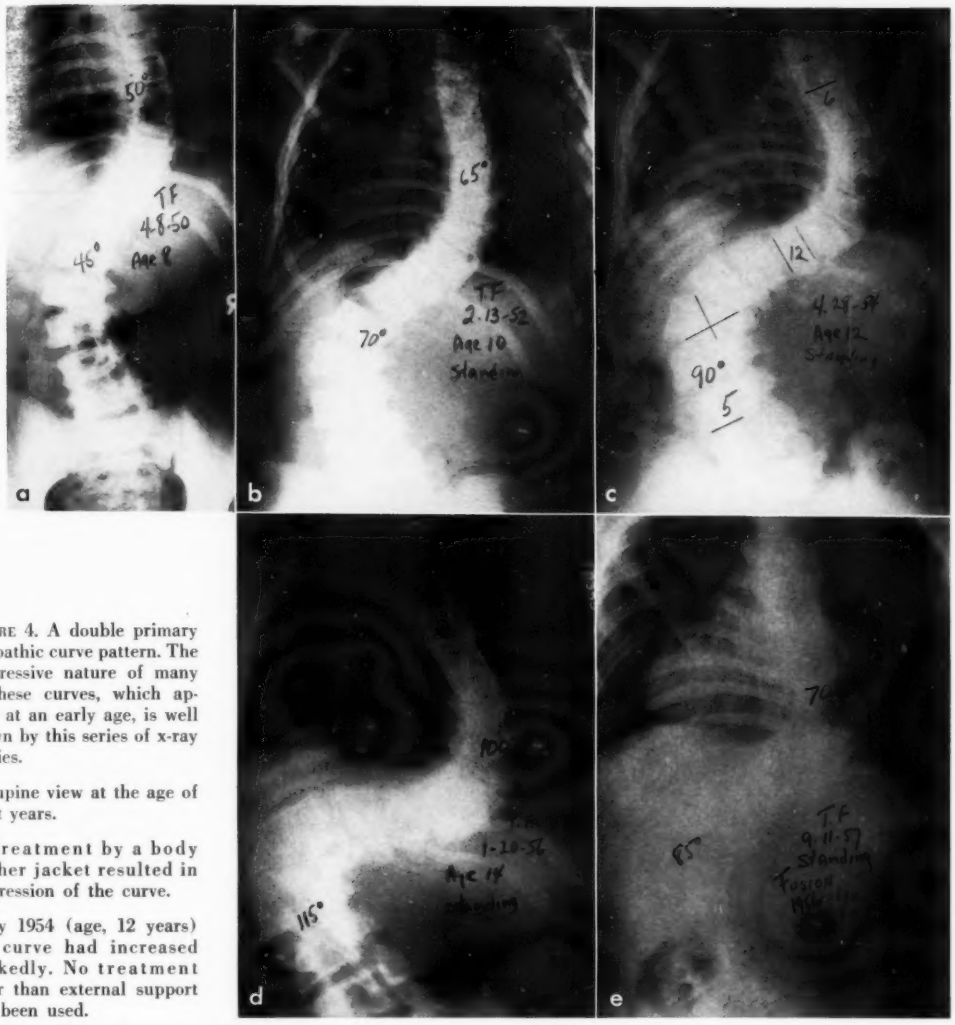


FIGURE 4. A double primary idiopathic curve pattern. The progressive nature of many of these curves, which appear at an early age, is well shown by this series of x-ray studies.

a. Supine view at the age of eight years.

b. Treatment by a body leather jacket resulted in progression of the curve.

c. By 1954 (age, 12 years) the curve had increased markedly. No treatment other than external support had been used.

d. By 1956, at the age of 14 years, the curves measured 100 degrees in the right thoracic area and 115 degrees in the left lumbar area.

e. One year after partial correction and fusion the curves measured 70 degrees above and 85 degrees below, bringing him back to the curves present in 1953. The desirability of correcting these curves early, before irreversible changes take place, is well illustrated.

growth changes in the vertebral bodies and to similar changes in all structures attached or related to the spine. The vertebral bodies become wedged and distorted, the soft tissues become deranged, and the rib cage becomes distorted with prominence on the convex side of the curve posteriorly, also carrying the overlying scapula into greater prominence. There is a corresponding depression of the ribs on the concave side, and the front of the thorax becomes asymmetrical. In the lumbar area, vertebral rotation carries the transverse processes and the attached muscles into prominence on one side and into depression on the other. Clinically, rotation is best demonstrated

FIGURE 5. This girl, 14 years and nine months of age, is well balanced and does not appear markedly deformed, although she has a right thoracic curve of 80 degrees and a left lumbar curve of 75 degrees. There are also curves above and below these two center curves. No treatment was given in this instance, but correction and fusion are advisable in most curves of this severity.

by having the patient bend forward (figure 2).

The amount of such structural changes depends on the degree of angulation of the curve and on the amount of rotation. In severe curves showing an angulation of over 100 degrees, the thorax becomes so deformed that cardiac and respiratory functions may be embarrassed, sometimes to the point of cardiac decompensation and failure (figure 3).

When a curve appears, the spine bends above and below it in the opposite direction, seeking to maintain body balance by a physiologic response known as the "righting" reflex. The primary curve is thus accompanied by secondary or compensatory curves. There is most often a middle primary curve with compensatory curves above and below, or the primary thoracic curve may be balanced by an equally angulated lumbar curve, these being further balanced by short curves above and below, forming a quadruple curve pattern. Sometimes two primary curves appear simultaneously, forming the same quadruple curve pattern (figure 4).

The primary curve in scoliosis is usually the center one of three curves or the center two of four curves. It is usually the most rigid and structural and it is often longer than the compensatory curves. Unless x-ray studies are available from the onset of the deformity, it is difficult to determine whether the patient has a double primary curve pattern or whether the compensatory curve became structural to a similar degree.

The secondary or compensatory curves often remain flexible to a marked degree, sometimes completely so. It is probable that those becoming increasingly structural do so because they are subjected to the same type of deforming influences which are acting on the primary curve.

When the spine is able to maintain itself in complete balance, the upright patient will be able to demonstrate body balance or compensation. The shoulders and pelvis will be level with the floor and with each other. A plumb line dropped from the occiput will bisect the sacrum. Such perfect balance will occur usually in the presence of multiple short curves (figure 5).

Since treatment of lateral spinal curvatures is based primarily on the cosmetic appearance, the ability of the spine to produce complete compensation becomes important in outlining treatment. Mild to moderate curves, if well compensated, may produce so little cosmetic deformity that they are not noticeable. Such curves, if nonprogressive, do not require treatment other than correction of any existing postural defects through exercise. As Steindler[1] has demonstrated, it is possible through supervised exercise and bracing to regain compensation in some of the more severe curves, thereby improving the patient's appearance. However, the more severe curves treated by this approach do not show cosmetic improvement in any way comparable to that obtained by actual correction of the curve

FIGURE 6a. A 45 degree idiopathic curve which is visible only on the closest inspection. Treatment is not indicated since the iliac apophyses have completed their excursion and the curve will not progress further.

b. A 30 degree idiopathic curve which is longer and therefore is moderately deforming. The deformity is not severe enough to urge correction and fusion. Note that although the curve is of less angulation it is more deforming than that shown in figure 6a.

and maintenance of such correction by spinal fusion.

Decompensation occurs when the spine is unable to produce balance within itself. Such decompensation is manifested by a listing of the body toward the convex side of the primary curve, by a tilting of the pelvis so that the highest side is on the concavity of the primary curve, and by a dropping of the shoulder downward on the same side that the pelvis is raised. When decompensation occurs in scoliosis, the body becomes grossly distorted. Associated with decompensation in producing severe deformity is the factor of rotation of the vertebral bodies so that body distortion becomes extreme. Any one of the factors mentioned may produce decompensation; for example, in a high cervicothoracic curve often seen in patients who have had poliomyelitis, there is no list or pelvic obliquity but there is severe deformity produced by the upper ribs becoming prominent into the neck and by the dropping of the shoulder. It is axiomatic that a long curve produces more deformity than does a short curve, and long curves of relatively mild angulation may demonstrate decompensation by a body list. Because of this variable appearance which curves of various lengths may produce, no rule can be established regarding the degree of angulation which requires active treatment (figure 6).

X-rays in Scoliosis

The true progress and evaluation of a lateral curvature can be ascertained only by x-ray studies. In the training of technicians, most roentgenologists teach that bone detail in spinal studies is of greatest importance and hence such studies should be made on small films by the spot technic. Such films are of no value in the study of scoliosis, for they do not show the entire curve on any one film. Further, they are routinely taken with the patient supine. If an evaluation is to be made of the scoliotic spine, the roentgenologist and his technician must be specifically instructed as to the size of the films required and the method by which they should be taken.

All x-rays of the scoliotic spine should be on 14 by 17 in. film. The technician should have on hand cassette markers indicating clearly whether the x-ray is taken supine, sitting or standing. The technician should receive specific directions as to the area of the spine encompassed by the curve. If such directions are not available, the technician must be

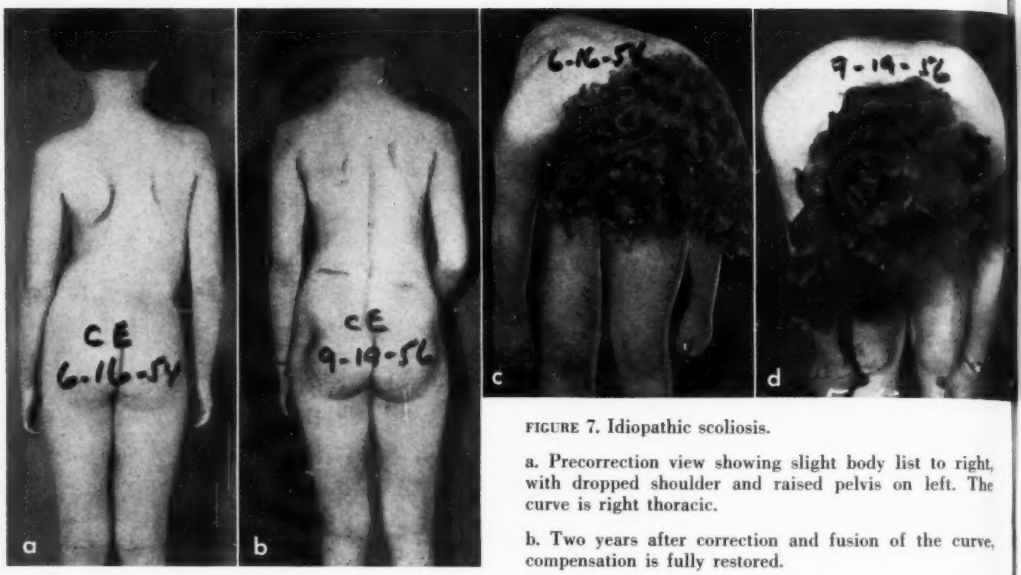


FIGURE 7. Idiopathic scoliosis.

a. Precorrection view showing slight body list to right, with dropped shoulder and raised pelvis on left. The curve is right thoracic.

b. Two years after correction and fusion of the curve, compensation is fully restored.

c. Precorrection rib deformity due to rotation.

d. Correction of curve has diminished rib deformity.

resourceful enough to ascertain the area of the curve by observing the patient. In smaller patients the entire spine can be visualized on one 14 by 17 in. film; in large patients it is necessary to take separate films of each curve.

When the scoliotic patient is first seen, the following x-rays should be taken as a routine:

1. Supine, sitting and standing anteroposterior views on 14 by 17 in. film showing the entire spine or, in larger patients, showing each curve separately. This study requires either three or six separate films.

2. Side-bending films with the patient supine and bending actively and with some force, first to show the amount of straightening possible of the primary curve, and secondly to show the amount of straightening possible of the compensatory curves above and below the primary. One film of the primary curve is sufficient; two films are necessary to show straightening of the compensation curves in larger patients.

3. Lateral views of the spine should be taken in the supine position when the patient is young and still growing. The lateral view is of value only in determining the anteroposterior diameter of the chest and to note tendencies toward flattening or lordosis of the thoracic spine. The lateral view can be routinely omitted in older patients who are through growing.

4. The upper portion of the pelvis must be included in one of the anteroposterior views of the spine so that the appearance and extent of excursion of the iliac apophyses can be visualized. It may be necessary to take a separate film for this purpose.

X-ray studies of scoliotic patients at intervals over a period of years may result in accumulation of a dangerous amount of radiation exposure. For this reason, it is extremely important to take only the films necessary and to take them properly with the first attempt.

When a curve's progress is being followed by x-ray studies every three or four months, the primary curve only should have an anteroposterior view with the patient standing or sitting. Further side-bending films may be needed at long intervals.

Etiology of Scoliosis

There are three classifications of lateral curvature which account for over 90 per cent

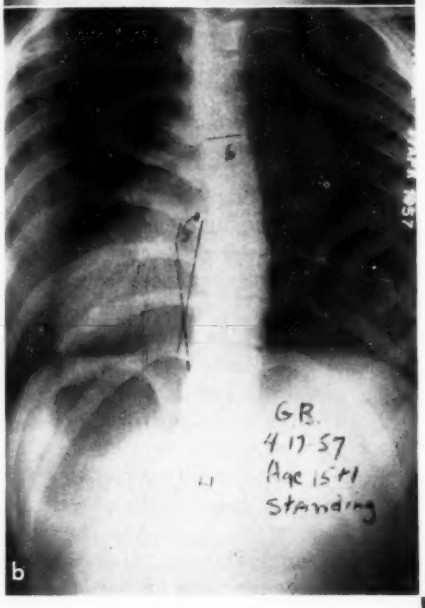


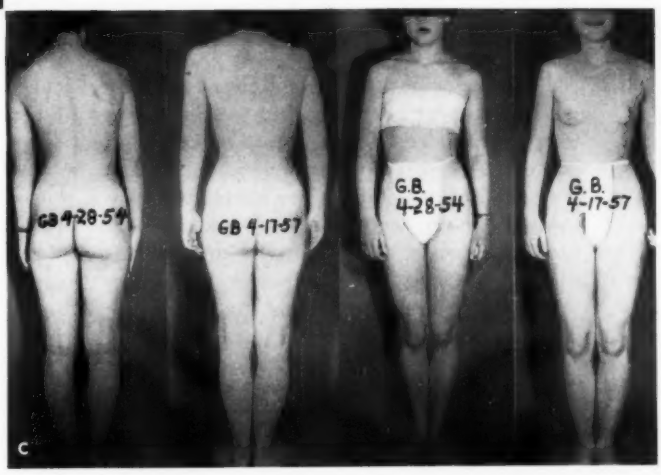
FIGURE 8a. A 25 degree right thoracic idiopathic curve in a 12 year old girl.

b. Three years later, at the age of 15 years, the curve has diminished spontaneously to 15 degrees, standing. No treatment had been carried out or advised.

c. Photographs of the patient at the ages of 12 and 15 years.

of all cases of scoliosis: idiopathic curves, curves secondary to muscular imbalance from poliomyelitis, and curves due to congenital vertebral anomalies. Other causes of scoliosis are growth distortion from neurofibromatosis, arachnodactyly or Marfan's syndrome, pleural fibrosis following empyema, growth disturbance from vertebral fractures or from rib resections of the costotransverse process region, muscular imbalance associated with spastic paralysis, and other rare conditions. Rickets, once thought to be a common etiologic agent in producing scoliosis, is seldom if ever the cause of lateral curvature.

Idiopathic scoliosis appears to be a clinical entity of unknown causes (figure 7). More than 85 per cent of the patients are girls. It usually appears at about the age of 11 or 12 years, although it may appear much earlier. It may be found in siblings, and not infrequently there appears to be a hereditary tendency in the family history. Many idiopathic curves remain of such mild degree that they escape notice unless searched for. For this reason, the proportion of such curves in the general population as well as the percentage of idiopathic curves which progress to a deforming degree remain somewhat controversial. Following a study of several thousand scoliotic patients and their families, Cobb[2,3] concluded that only a small percentage of idiopathic curves progress to a deformity sufficient to warrant active correction. There is general agreement that the earlier the curve appears the more likely it will progress to a severe deformity. An entity known as infantile idio-



pathic scoliosis has been described in England which demonstrates a preponderantly left thoracic curve in early infancy and progresses to a severe kyphoscoliotic deformity during childhood and adolescence (figure 8).

The progression of idiopathic curves varies. Scoliosis is a deformity of growth; the deformity will not appear after spinal growth is complete, and there is a strong tendency for all lateral curvatures to stop progressing when spinal growth is complete. This is particularly true of idiopathic scoliosis. A sign indicating the end of spinal growth is of clinical importance in scoliosis, and Risser's[4,5] sign of the iliac apophyses gives us this information. The iliac apophysis appears on an x-ray of the pelvic brim as a line of ossification paralleling the brim of the pelvis, progressing from the anterior superior spine to the posterior superior spine. When it has completed its excursion and has made contact with the ilium at the posterior iliac spine, spinal growth can be considered essentially complete. It is not necessary for the apophysis to show complete closure, for this takes place slowly over a period of years.

Risser advanced the thought that idiopathic scoliosis is of metabolic origin, associated in some manner with an essential nutritional deficiency. No proof of this exists, and an interesting observation from India indicates the rarity of idiopathic scoliosis in that country of widespread malnutrition. The diagnosis of idiopathic scoliosis must necessarily be somewhat inexact, for such curves may appear in patients who have had a possible nonparalytic poliomyelitis.

Idiopathic curves are of a right thoracic or right thoracolumbar pattern in 70 per cent of cases. The next most common pattern is the left thoracolumbar.

Paralytic or postpoliomyelitic scoliosis may make its appearance soon after the disease or many years later. Muscle testing may demonstrate muscular weakness somewhere in the body, and in the majority of patients the muscular imbalance is obvious. The muscles which play the greatest role in producing scoliosis through their inequality of power are the anterior and lateral abdominals and the intercostals. Soft-tissue contractures below the pelvic brim such as hip flexion and iliotibial band contractures may produce fixed pelvic obliquity and thereby contribute to the scoliosis. Paralytic curves tend to be longer and more collapsing than other types of scoliosis. They tend to progress severely, and conservative treatment is of little help in controlling the curve (figure 9).

Congenital scoliosis encompasses a great variety of abnormalities of the spine ranging from the single hemivertebra to the most bizarre malformations of spine and ribs. Unsegmented blocks of the lateral masses of the vertebrae are often seen at the apical concavity of a curve, usually with a group of fused ribs attached thereto, while on the convex side there will be relatively normal segmentation and rib formation. Such findings obviously indicate the reason for the curve. One curve-producing abnormality may be balanced by an opposite similar abnormality, the net result being a balanced spine showing little tendency toward progression of the curve. When hemivertebrae lie posteriorly displaced, there appears to be a marked although not universal tendency toward progression during growth to a very severe kyphoscoliosis. Spina bifida is frequently present, particularly in the lumbar or sacral spine, and may be associated with formation of myelomeningocele and with paresis or paralysis of the lower extremities. A paresis, often with clubfoot deformity, may also be found in the rare congenital anomaly known as diastematomyelia. Here the intraneural space between the pedicles is widened; a spur of bone projects from the dorsal central vertebral body, bisecting the dura. A traction syndrome on the cord results, because, as the spine grows, normal ascent of the cord is prevented and progressive muscular weakness and deformity in the lower limbs occur. Such anomalies are usually accompanied by others associated with scoliosis.

The prognosis of congenital scoliosis is variable. Many hemivertebrae at the dorsolumbar area do not progress severely, and many balanced anomalies likewise may not require treatment. In none, however, can a positive prognosis be given, and all have to be

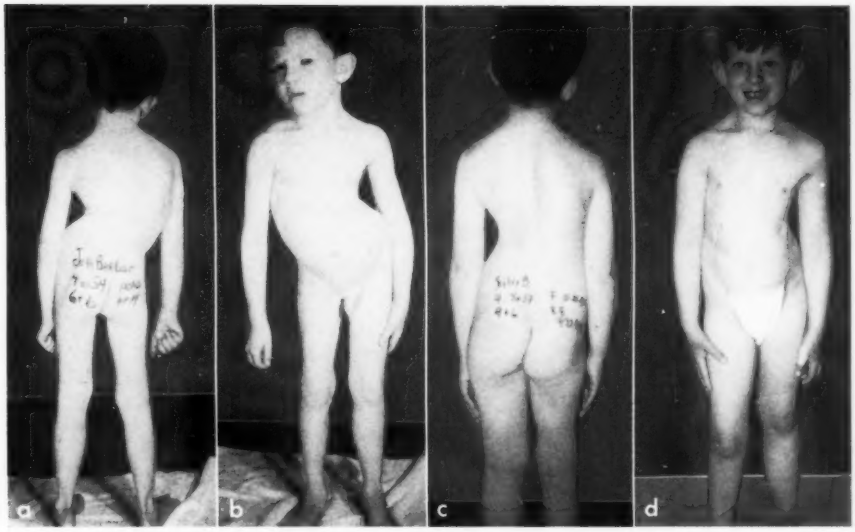


FIGURE 9. Paralytic scoliosis due to poliomyelitis.

a and b. Precorrection views of a six year old boy with a severe paralytic curve.

c and d. Three years after correction and fusion of the curve. The initial curve was 135 degrees, and the final curve was 55 degrees.

watched carefully during growth. A severely deforming curve can often be gradually straightened during infancy and childhood, giving a better cosmetic result than that obtained by fusion in infancy. As a general rule, however, congenital curves should be given maximal correction and fused early in life, for a great majority cannot be controlled by conservative means.

Treatment of Scoliosis

Conservative measures to control or improve scoliosis have been foremost in the minds of a majority of orthopedic surgeons for many decades. Steindler's experiences with correction and fusion of lateral curvatures at the University of Iowa, only recently reported by Ponseti and Friedman[6,7] in 1950, led him to feel, with justification, that the most important aspects of treatment of scoliosis were preservation and re-establishment of compensation. The Steindler "shift" exercises, the Steindler brace and the conservative approach to the problem dominated the field of scoliosis therapy during the 1930s and 1940s. Along with general mobilizing exercises to keep the spine limber, this same approach to the scoliotic problem still is foremost in the mind of the physiatrist as well as in the minds of a substantial percentage of orthopedic surgeons.

In 1924, when Russell Hibbs[8] reported his experience with fusion of the curved spine in the first 59 cases, a great deal of controversy arose concerning the need for such a drastic procedure as well as the dangers involved and the results obtained. In this first report, Hibbs freely admitted that in many of his early cases fusion was done without correction.[9] He noted that those patients fused in their late teens did not have further progression of the curve after fusion, while in those fused at a much earlier age the curve sometimes increased after fusion. His average period of cast immobilization, even in those patients given active correction, was only three or four months. We now know that his older patients did not have progression of the curve after fusion because they were through growing, and that the curvature increased in the younger patients because they did not have a solid and mature fusion at the time they were allowed up with inadequate or no external support.

Nevertheless, Hibbs remained enthusiastic toward his treatment of scoliosis by correction and fusion of the curve. With the help of Risser, the corrective wedging or turnbuckle cast became an excellent method of correction. With the help of Ferguson, increasing knowl-

edge was gained concerning the required length of the fusion area, the strength and maturity of the graft necessary to maintain correction, and the detection of pseudarthroses in the graft. When Hibbs, Risser and Ferguson[10] reported the first large series of scoliotic patients treated by correction and fusion of the curve in 1931, their conclusions showed continued enthusiasm toward this form of treatment as the only way the curve could be actually corrected. Unfortunately, except in the hands of a few orthopedic surgeons who continued to carry out the painstaking technic of Hibbs and Risser, the method met with decreasing enthusiasm among those who sought short cuts in the fusion technic and who did not appreciate the length of time required for a fusion to become solid and mature enough to withstand the deforming forces inherent in a structural curve.

At present, there is a growing number of orthopedic surgeons who have persistently battled their way along the hard road of experience in the treatment of scoliosis by correction and fusion. Through their cooperative efforts, great advances have been made in ascertaining and overcoming the errors which lead to loss of correction in the fused curve. We know now that if these pitfalls are avoided the treatment of scoliosis by correction and fusion is eminently successful. What, then, are the requirements which the general practitioner or the orthopedic surgeon must know in order that both he and his scoliotic patient will be happy and satisfied?

He must appreciate that many curves progress only to a mild and nondeforming degree and not urge treatment by fusion in a mild curve until it is established through periodic upright x-ray studies that the curve is progressive. He must know that it is the idiopathic curve which is most likely to be nonprogressive and that most paralytic curves will progress to a deforming state.[11,12] He must know that most curves and nearly all idiopathic curves do not progress after spinal growth is complete.

On the other hand, he must not be guilty of undue procrastination in regard to correction and fusion of a progressing curve. He must know that in many curves irreversible structural changes may occur rather rapidly and that the golden opportunity for excellent correction may be easily overlooked while watching the curve.

He must know that application of body braces to prevent progression of a curve which is inherently progressive is of limited value. Only casts or braces which actively correct the curve, such as the Milwaukee brace of Blount[13] and Schmidt[14] or the Risser localizer cast, will maintain any active correction when the patient is upright and ambulatory, such correction being maintained by distraction between head and pelvis plus lateral pressure against the convexity of the curve.

He must know that the chief value of treatment by stretching and exercise lies in the maintenance of flexibility and the improvement in postural appearance in the milder curves; that no inherently progressive curve can be kept from progressing through stretching, exercise or postural training; that only through improvement in compensation is the patient's appearance improved by any exercise program. He must know that the occasional idiopathic thoracolumbar curve can be shortened and sometimes lessened in angulation by having the patient wear a high shoe lift on the convex side of the curve, creating an artificial pelvic obliquity during the growing years. *He must not place undue credit on any form of conservative treatment of mild, flexible idiopathic curves,* knowing that many of them do not inherently progress and that occasionally one sees improvement in the angulation of the curve during growth without treatment (figure 8).

He must know that in poliomyelitic curves the reinforcement of weak or absent abdominal muscles by the insertion of tight bands of fascia lata between ribs and pelvis gives a marked balancing effect to the torso and helps to maintain the curve in balance but usually does not obviate the need for correction and fusion of the curve. *He must also know that all hip flexion and abduction contractures below the pelvic brim produced by a tight iliotibial band and other soft structures must be released before proceeding with the correction and fusion of the curve* (figure 10).

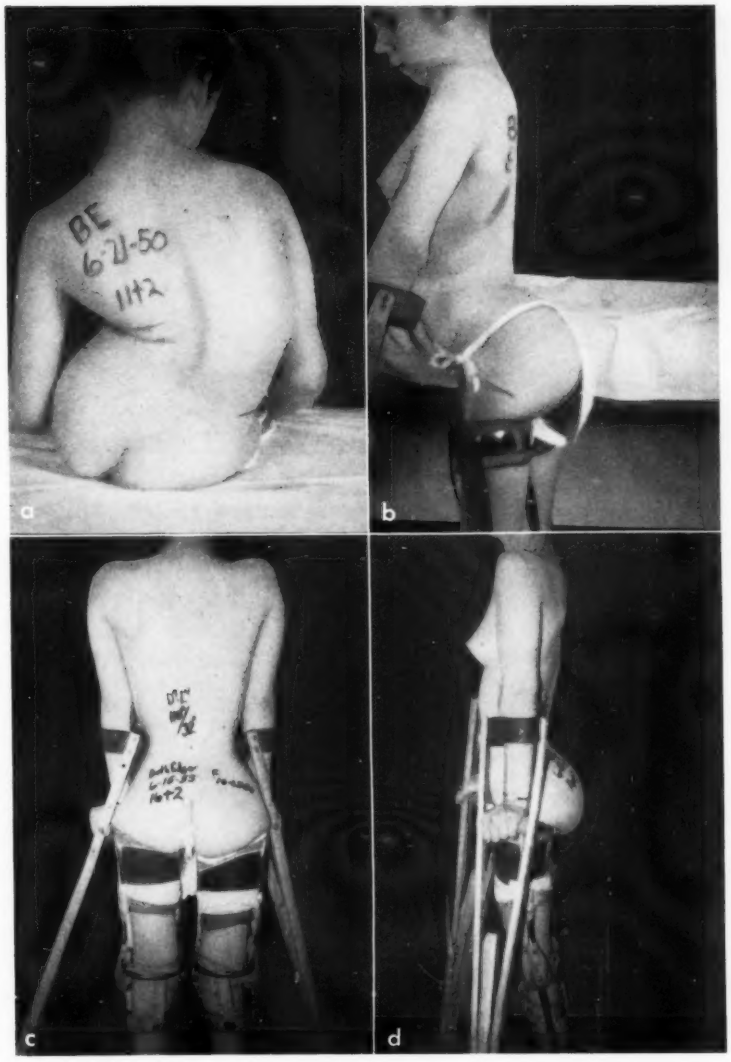


FIGURE 10. Postpoliomyelitic scoliosis with severe flexion contractures of hips.

a. Age, 11 years. Curve, 110 degrees. Severe pelvic obliquity and severe flexion contracture of hip, due to contracture of iliotibial bands primarily.

b. Severe lordosis was present. The hip flexion contracture was nearly 90 degrees.

c. Correction of the contractures of the iliotibial band and hip were done by open surgical release, followed by postoperative stretching in plaster. Thereafter the curve was corrected and fused in a turnbuckle cast. The result five years later is shown.

d. Side view which shows the elimination of most of the lordosis.

He must know that maximal correction of the curve can be obtained and maintained only in the supine position, and that such correction can be maintained without external support only by a fusion which is long enough, solid beyond question, and made up of mature, unyielding bone. He must know that the time required for the formation of such a graft will average 10 months.

He must maintain constant vigilance in the search for and recognition of pseudarthroses, that archenemy which can so insidiously undo the good work that has been accomplished. He must know that a chain is only as strong as its weakest link, that complete loss of correction can occur through the development of one graft defect, that recognition and repair of pseudarthroses before external support is removed will prevent such loss of correction, and also that recorrection of loss from an unrecognized pseudarthrosis can usually be carried out.

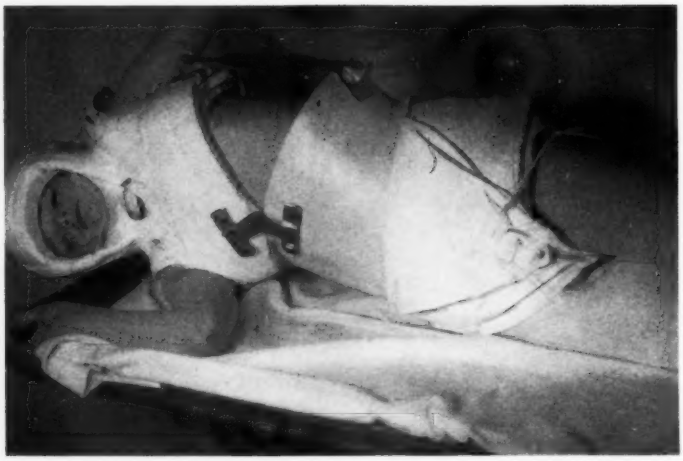


FIGURE 11. Risser turnbuckle cast for correction of lateral curvature of the spine.

Methods of Correction

The mechanical principles underlying all effective corrective appliances for scoliosis are those of distraction combined with lateral pressure against the apex of the curve. Risser, working with Hibbs, developed a very efficient turnbuckle cast, which, by eccentrically placed hinges, provides both distraction and lateral bend (figure 11). Blount[13] and Schmidt,[14] working together on a means of obtaining both distraction and lateral pressure against the curve, developed the very efficient Milwaukee brace (figure 12). Risser recently incorporated the mechanical principles of this brace into a cast application on a special frame known as the Risser localizer cast. This is fast becoming the most popular method of cast correction of scoliosis (figure 13). When snugly applied with a minimal amount of padding, this cast provides a means of ambulatory correction of the curve with only slight to moderate loss from the maximal supine correction. For maximal correction, the patient is kept supine for five months, after which the fusion is usually solid enough to allow ambulation in a snugly fitted localizer cast. External protection is provided until the fusion is unquestion-

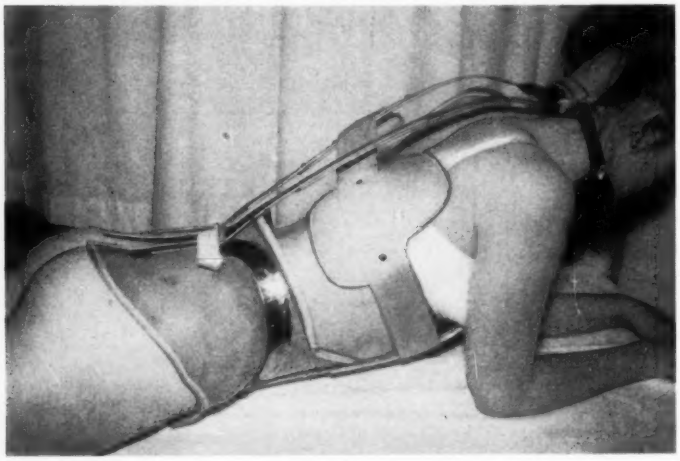


FIGURE 12. Milwaukee brace of Blount and Schmidt.

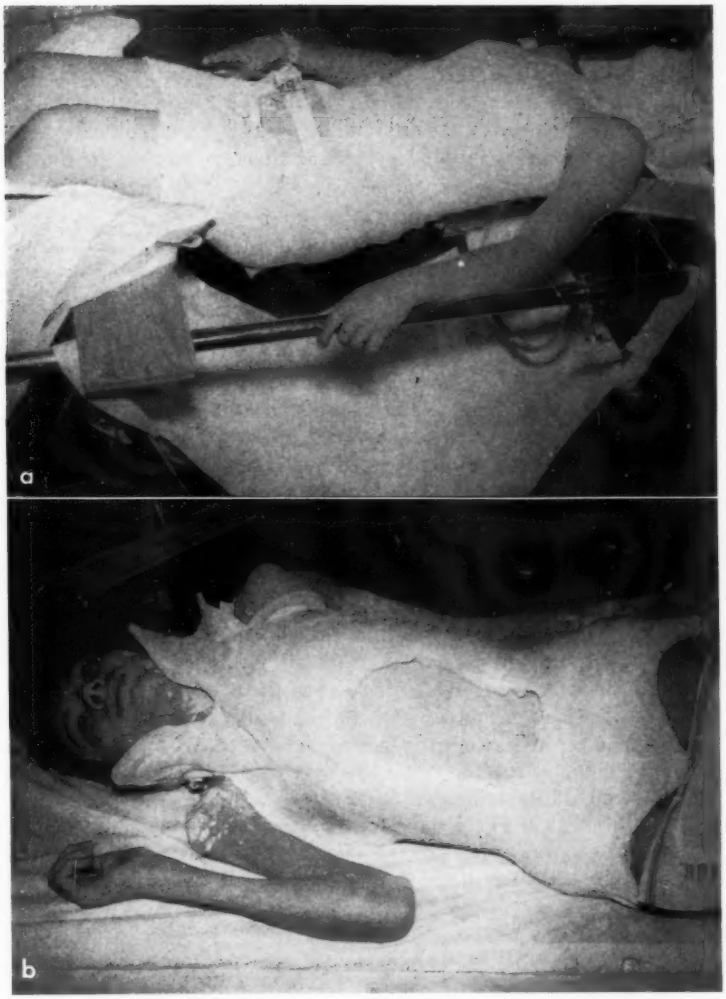


FIGURE 13. Risser localizer cast.

a. Application of the cast.

b. Completed cast.

ably solid and mature, usually 10 to 14 months after the operation.

Measurement of Curve Angulation

The easiest and most popular method of measurement of curve angulation was described by Cobb.[3] The maximally tilted vertebra at the top of the curve is selected and a line is drawn as accurately as possible on its superior vertebral border. At the lower end of the curve the maximally tilted end vertebra is again selected and a line is drawn across its lower vertebral border. From these two lines, perpendiculars are erected which will cross. The angle is then measured with a transparent protractor. By this method or any method of x-ray measurement of the curve, there is a margin of error of about 5 degrees.

The Fusion Operation

With present-day anesthesia and blood replacement, extensive fusions can be carried out safely, although the procedure must still be divided into two or three stages when the area to be fused comprises 10 or more vertebrae. Studies of various methods of perform-

ing fusions have shown quite clearly that subperiosteal meticulous exposure of the entire dorsal surface of the vertebra, including the joints and transverse processes, combined with effective destruction of the individual joints, preferably by inserting blocks of cancellous bone into each joint, plus complete decortication of the entire exposed surface with the creation of free or attached interweaving fragments of bone, gives the best fusion bed.[15] To effect the highest percentage of solid fusions, additional bone is necessary, especially below the tenth thoracic vertebra. Autogenous bone has been found to be superior to banked bone. With such a carefully executed fusion procedure, one can expect to obtain a pseudarthrosis in about 6 per cent of idiopathic curves and in about 15 per cent of paralytic curves. As previously pointed out, a graft defect can be discovered when the fusion is carefully evaluated five or six months after surgery, at which time repair of the defect should be done.

Hibbs, who performed the first spinal fusion in 1911 and whose meticulous technic of facet fusion was described in 1924, has provided us with an example of technical skill and ingenuity in performing spinal fusions which is difficult to equal.

Conclusions

Conservative treatment of a progressive lateral spinal curvature will not be effective. Curves which are progressive, as shown by upright x-ray studies, should be actively corrected and fused. The end results of such correction and fusion, when properly performed, are entirely satisfactory and the procedures can be carried out at whatever age necessary without fear of growth disturbance or other ill effects. Those who have had extensive experience with such active correction of scoliosis agree that in no field of medicine will one find a more appreciative patient than the one whose twisted torso has been straightened.

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Studies of Cardiac Output During the Early Phase of Rehabilitation

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For the patient who has just experienced acute myocardial disease or injury a program must be planned which will eventually restore him to the greatest usefulness which is possible with his damaged heart. In view of the fact that 85 per cent of patients survive an acute episode of myocardial infarction,[1] the initial care of cardiac patients should include the beginning steps of a rehabilitation program, anticipating the return of the patient to his home and usually to employment. The program of restoration is long and involved. The physician must make many decisions regarding the activities which the patient may perform through the acute and convalescent stages of his illness, as well as the limitations he must observe when he can return to work. These decisions are not easy to make because of the complexity of the problem. There is scanty knowledge concerning the work that the heart must do under varying conditions of activity in or out of the hospital. Since the work of the heart is influenced by both metabolic work and emotional stress, the actual work load is not readily apparent. Factors such as the posture during work, the muscles being used, the variation of muscular activity required to support the trunk or extremities in varying attitudes of work, and the high metabolic work requirement during elevation of the body or extremities all make the evaluation more difficult.

There has been a tendency to try to protect the cardiac patient by restricting him to such a low level of activity in work and recreation that there will be minimal stress on the myocardium. This type of restriction produces psychogenic invalidism in many cardiac patients for fear that further damage may occur. On the advice of their physicians, some patients so restrict their physical activities that they remain dependent for the rest of their

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lives. This results in an unsatisfactory existence for the patient and an even more unsatisfactory situation for the patient's family. However, even these patients do perform activities which are necessary when living at home, activities which require much greater metabolic and cardiac effort than others from which they have been restricted. Because of our incomplete knowledge regarding the cardiac stress produced by various daily activities, the restrictions placed on cardiac patients are not systematically uniform and, in many cases, are unrealistic. Necessary daily activities of bathing, dressing and stair climbing are permitted at the same time that vocational activities causing much less cardiac stress are banned. Hellerstein and Goldston[2] found that 76 per cent of cardiac patients in the Cleveland Work Classification Clinic were able to return to the same vocational and occupational classification as that prior to their illness.

The maximal cardiac output can be measured with some degree of accuracy only when the heart is working maximally. If the heart is working below full capacity the reserve capacity cannot be estimated reliably. Berggren and Christensen[3] reported that for a normal individual in a constant posture, working at a nonfatiguing rate in a steady state on a given day, with a uniform type of work, a linear relationship exists between pulse rate and oxygen consumption. In normal healthy adults the maximum cardiac rate was 190 beats per minute. If pulse rate and oxygen consumption were measured at two or more levels of activity, linear extrapolation to a pulse rate of 190 provided an estimate of that person's upper metabolic limit. Whether this upper limit of cardiac rate or the linear relationship between the pulse and metabolism applies to patients with cardiac damage has not been determined.

Simple clinical methods are not available to measure the work of the heart during physical activity. In the laboratory, cardiac output may be measured following cardiac catheterization by the direct Fick method or by methods based on dye dilution or foreign gas uptake. For clinical use less direct and less quantitative methods must be used. The comparison of pulse rates during work with maximal pulse rate,[3] the response of the pulse, blood pressure, electrocardiogram or respiratory rate during a standard activity,[4,5] and the postergal decline of pulse rate to the resting level[6] provided information regarding the ability of the heart to respond to or to recover from the stress of work.

The three methods for estimating cardiac output—cardiac catheterization, dye dilution and foreign gas uptake—give similar results. Although there has been criticism[7] of the acetylene method[8] of estimating arteriovenous oxygen difference, studies by Asmussen and Nielsen[9] and by Chapman and associates[10] show a high degree of correlation between the methods. Chapman found the acetylene method approximately 24 per cent lower than the direct Fick method, due to an incorrect solubility factor for acetylene, recirculation of acetylene, and increased oxygenation of arterial blood during rebreathing. During work experiments with cardiac output up to 22 l. per minute, the acetylene and dye injection methods gave identical values with smaller percentage standard deviations during work than at rest.[9]

Cardiac output or oxygen consumption has been studied for only a few hospital or rehabilitation activities.[11-13] For many of these activities it has been assumed that cardiac work is linearly proportional to oxygen consumption. If further work proves this assumption valid information concerning oxygen consumption during normal daily activities, work or recreation can be used directly to estimate the cardiac work.[14,15] However, it appears that the relationship between metabolic work and cardiac work is not linear under all conditions. Most of the published data concerns the mean oxygen consumption over an extended period of time. From it no information can be obtained concerning fluctuations of oxygen consumption or variations of blood pressure which change the stress on the heart. During normal activities the rate of oxygen consumption does fluctuate, especially when there are changes of posture or of the work load. Transient large increases of oxygen uptake and cardiac work during activities which otherwise have a low metabolic demand may produce the stress causing myocardial failure in patients with heart disease.

A series of studies has been carried out to obtain information concerning the requirements for cardiac output of various types of activities commonly performed by cardiac patients in the hospital or during convalescence. These studies were done on healthy young women who were accustomed to the laboratory procedures and were acquainted with the activities which they were requested to perform. For a number of selected activities the mean oxygen consumption and cardiac output were determined after the subject had reached a steady state in her work. Studies were also made of the fluctuations of oxygen consumption and periodic arteriovenous oxygen differences during activities commonly performed by patients and which are obviously phasic in their energy demands. For these activities an attempt has been made to estimate the peak requirements for metabolic and cardiac work.

Methods

The methods for determining mean oxygen consumption and the acetylene method for estimating mean cardiac output while the subject was working at a "steady state" have been described previously.[11] For the studies of phasic variation in metabolic effort during the activities investigated, methods for rapid analysis and recording of oxygen concentration and carbon dioxide concentration in expired air, respiratory minute volume, and pulse rate were utilized. The data were computed electronically to provide a continuous record of oxygen consumption. The subject inspired room air through a valved mouthpiece and expired through a hose 1 in. in diameter connected to a large spirometer. Respiratory minute volume was recorded electronically from the motion of the spirometer. A sample of mixed, expired air was pumped continuously through a Beckman Model F3 oxygen analyzer and a Beckman infrared carbon dioxide analyzer from which the concentrations of oxygen and carbon dioxide were recorded. These data were inserted into a Brown electronic variable span recorder with a retransmitting slide wire to compute and record continuously the oxygen consumption rate of the subject. With this system there was a lag of a few seconds between the time of expiration of air and the time of analysis, but the response time of the recorders to accurate levels was probably less than 15 seconds. Even when changes were faster than this, although accuracy was diminished, the trends were clearly shown. The arteriovenous oxygen difference was obtained periodically by the acetylene method.[10] It is necessary to allow an interval of 30 minutes between the acetylene rebreathing tests to clear absorbed acetylene from the blood. Therefore, the arteriovenous oxygen difference could be checked only at intervals of 30 minutes rather than repeatedly during the peaks of oxygen consumption. The calculated cardiac output, in these cases labeled "presumptive cardiac output," is based on the arteriovenous oxygen difference determined after the activity has been carried on for a period of time. The speed or extent of fluctuation of arteriovenous oxygen difference during fluctuation of oxygen demand is unknown. The calculated cardiac output will represent the true cardiac output only to the ex-

TABLE 1

EFFECT OF POSITION ON THE MEAN CARDIAC OUTPUT OF NORMAL YOUNG WOMEN

POSITION	SUBJECTS	TESTS	CARDIAC OUTPUT L./MIN./1.65 M.^{2}	σ	PER CENT INCREASE OVER SUPINE
Supine	18	207	4.07	1.59	
Seated on straight-backed chair	9	127	3.82	1.40	–6
Seated on edge of bed with feet supported	3	19	3.92	0.30	–4
Semireclining at 45 degrees with knees up	5	59	4.50	0.31	11

tent that arteriovenous oxygen difference tends to change slowly. The pulse rate was recorded from a Waters cardiotachometer.

All studies were carried out on subjects in the fasting state who had rested for 30 minutes in the supine position on a hospital bed in the laboratory where there was minimal noise and distraction. At the end of the rest period, oral temperature, blood pressure and pulse rate were recorded. This resting state approaches the basal metabolic level for these subjects. In most of the experiments the arteriovenous oxygen difference was determined by the Grollman method at the end of the control period prior to the test activity under consideration. Then the subject assumed the position of the test and maintained this position without work while the oxygen consumption and arteriovenous oxygen difference were determined again. Finally the subject worked at the selected activity until a steady state had been achieved, when a third determination of oxygen consumption and arteriovenous oxygen difference was made. An interval of at least 30 minutes was allowed between acetylene rebreathing tests in order to allow excretion of acetylene which had been absorbed into the blood. For purposes of comparison which might have an application to the hospital situation, the standard position of reference is supine recumbency on a horizontal bed with the subject fasting, relaxed and rested. Both cardiac output and metabolic work have been corrected to and are presented as that of a young woman of average size, i.e., 1.65 M.^{2} surface area.

Results

It is widely recognized that postural changes do affect the heart and cause changes of the pulse rate. It has been widely, although not generally, assumed that the work of the heart is greater in the sitting position than in the recumbent position and that patients with acute myocardial damage should be kept in bed to afford the greatest possible rest to the heart. The cardiac output does change on assumption of the sitting position but with a decreased rather than an increased output.[16] In this case the change in cardiac output with change of posture is not related to the change of oxygen consumption. In these studies, even though the oxygen consumption increased on the average of 10 per cent above the supine level

TABLE 2

EFFECT OF POSITION ON THE OXYGEN CONSUMPTION OF NORMAL YOUNG WOMEN

POSITION	SUBJECTS	TESTS	METABOLISM CAL./MIN./1.65 M.^{2}	σ	PER CENT INCREASE OVER SUPINE
Supine	56	365	0.97	0.10	
Semireclining at 45 degrees with knees up	5	60	0.95	0.09	–0.6
Seated on edge of bed with feet supported	3	19	1.04	0.11	7
Seated on straight-backed chair	62	318	1.07	0.16	10
Standing	16	47	1.11	0.14	15
Seated on high stool with forearms resting on table	17	47	1.18	0.16	22

FIGURE 1. "Dangling" is a position which reduces the work of the heart below that when the patient is lying or sitting in bed. Blood pools in the dependent legs and the venous return to the heart is reduced.

when the subjects sat on a straight-backed chair, the cardiac output decreased 6 per cent (tables 1 and 2). Patients sitting in a "dangling" position on the edge of the bed, with the feet supported but with no back support, had an average increase of oxygen consumption of 7 per cent but a decrease of cardiac output of 3.5 per cent (figure 1). On the other hand, there was no change of oxygen consumption from the supine level when the subjects sat in bed in a semireclining position, with the head, back and knees supported by a Gatch frame; yet the cardiac output increased 11 per cent (figure 2).

In appraising the cardiac work required by an activity, it is necessary to take into consideration the peripheral distribution of blood. Pooling of blood occurs in the dependent feet and legs, decreasing the venous return and the drive on the heart. Under such conditions cardiac output is decreased. If the patient is semireclining in bed with his knees elevated, not

FIGURE 2. Semireclining in bed with the knees elevated does not increase the oxygen consumption, but the mean cardiac output is increased 11 per cent over the supine level.

only is there a decreased dependent vascular bed in which pooling may occur but also there is compression of the splanchnic area to augment venous return, so that the cardiac output is increased. The patient in heart-failure who insists on dangling his legs over the side of the bed rather than semireclining has found that there is less cardiac effort involved, even though unsupported sitting does increase the

FIGURE 3. Sitting in an armchair with a high back, with full head, back and arm support and with the feet on the floor, is the position of minimal cardiac output and of near-basal oxygen consumption.

FIGURE 4. When a patient sits on a straight chair and uses only the hands and forearms for work, the average increase of the cardiac output is less than 25 per cent.

demand for oxygen. This patient can relax only when sitting in a chair with support for his head, back and arms but with his feet and legs dependent (figure 3).

The difference between cardiac output when recumbent and cardiac output when sitting is small. Probably it is only for patients in failure that this small difference is significant. Nevertheless, patients in failure do recognize that breathing is easier when they sit erect with the feet dependent. For other patients with myocardial damage, this position also affords the lowest demand for cardiac output. The rationale for early sitting by patients with coronary disease[17] has a sound basis.

Craft activities requiring the use of only the hands and forearms while the patient is sitting in a chair with his back and arms supported (figure 4) increase the cardiac output less than 20 per cent and can be considered very light activities (table 3). Similar activities performed while semireclining in bed fall into the same category of cardiac stress (figure 5). The mean percentage increase of oxygen consumption during these activities over that at supine rest is greater than is the mean percentage increase of cardiac output (table 4).

Activities which require muscular support for broad motions of the upper extremities or for balance of the body fall into a higher category of cardiac stress. Weaving on a floor loom requires a person to reach to arm's length and to shift the body on a backless bench during the weaving. The legs and feet are also moved on the pedals (figure 6). The mean metabolic rate during weaving on a floor loom was increased 112 per cent over the supine level (table 4). Cardiac output was increased 76 per cent over supine during this activity. The operation of a floor-model platen printing press also increased cardiac output 74 per cent. Printing on this press requires balancing, pedaling the press with one foot, and moving both arms with a fairly wide reach. Printing increased the oxygen consump-

TABLE 3

EFFECT OF VARIOUS ACTIVITIES ON THE MEAN CARDIAC OUTPUT OF NORMAL YOUNG WOMEN

ACTIVITY	SUBJECTS	TESTS	CARDIAC OUTPUT L./MIN./1.65 M.^{2}	σ	PER CENT INCREASE OVER SUPINE
Leather stamping, seated on chair	2	20	4.56	0.93	12
Chip carving, seated on chair	5	32	4.77	1.03	19
Leather tooling, seated on chair	4	15	4.83	2.24	19
Leather tooling, semireclining 45 degrees in bed	4	24	5.07	1.45	25
Running a printing press, standing	5	20	7.07	1.64	74
Floor loom weaving, seated on bench	2	18	7.15	1.86	76
Bicycle grinding, seated on bicycle saddle	3	25	9.98	2.51	145

FIGURE 5. Light activities on a bed table while semireclining increase the cardiac output very little at the same time that they divert the patient and decrease his emotional tensions.

FIGURE 6. Reaching at arm's length and leaning forward and back while operating a floor loom increase the mean cardiac output 76 per cent.

tion 133 per cent above the supine level. The cardiac output did not increase as much as the oxygen consumption because of an increase of the arteriovenous oxygen difference. These activities might be considered light activities.

Pedaling a bicycle grinder constituted the heaviest category of work studied here. In this activity the subjects pedaled at a rate of 12 rpm against a moderate resistance. The oxygen consumption increased 200 per cent above supine rest and cardiac output increased 145 per cent. Use of a handsaw required approximately the same level of oxygen consumption as did bicycling. These activities might be considered moderate in their energy requirement.

The studies of fluctuation of cardiac work

TABLE 4

EFFECT OF VARIOUS ACTIVITIES ON THE OXYGEN CONSUMPTION OF NORMAL YOUNG WOMEN

ACTIVITY	SUBJECTS	TESTS	METABOLISM CAL./MIN./1.65 M.^{2}	σ	PER CENT INCREASE OVER SUPINE
Leather tooling, semireclining 45 degrees in bed	4	24	1.09	0.12	12
Leather tooling, seated on straight-backed chair	17	41	1.28	0.24	32
Leather stamping, seated on straight-backed chair	14	38	1.33	0.16	37
Leather lacing, seated on straight-backed chair	11	27	1.39	0.18	43
Chip carving, seated on straight-backed chair	21	85	1.55	0.21	59
Leather carving, seated on straight-backed chair	12	44	1.65	0.23	70
Table loom weaving, seated on high stool	17	47	1.69	0.20	75
Floor loom weaving, seated on bench	2	24	2.05	0.24	112
Running a printing press, standing	5	26	2.26	0.28	133
Bicycle grinding, seated on bicycle saddle	6	35	2.91	0.32	200
Handsawing hardwood, standing	16	47	3.27	0.72	237

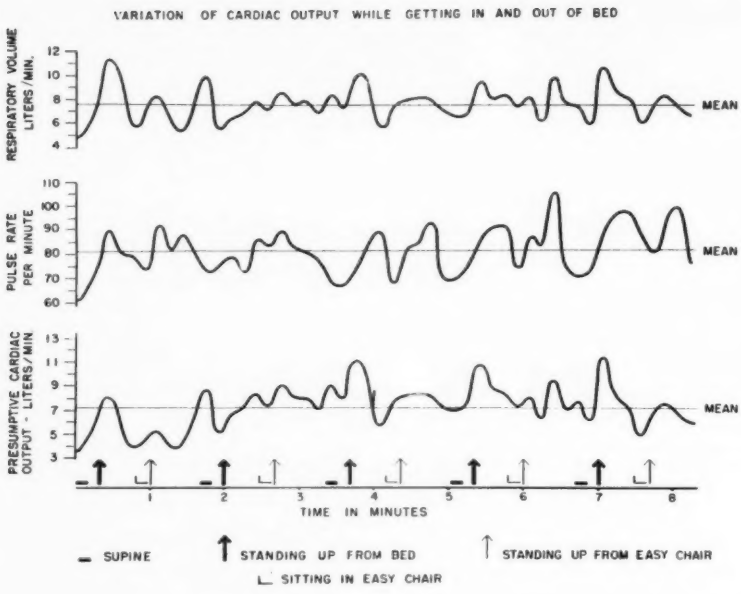
VARIATION OF CARDIAC OUTPUT WHILE GETTING IN AND OUT OF BED
RESPIRATORY VOLUME LITERS/MIN.
PULSE RATE PER MINUTE
PRESUMPTIVE CARDIAC OUTPUT - LITERS/MIN
MEAN
TIME IN MINUTES
SUPINE
STANDING UP FROM BED
STANDING UP FROM EASY CHAIR
SITTING IN EASY CHAIR

FIGURE 7. Response of the respiration, pulse and presumptive cardiac output of a normal subject to moving from a hospital bed to an easy chair and back without assistance. Presumptive cardiac output was calculated from the continuously recorded oxygen consumption and the arteriovenous oxygen difference obtained by acetylene rebreathing at the end of the activity. J. E. surface area 1.67 M².

during phasic activities revealed some interesting information. Of special interest was the observation that activity requiring elevation of the body produced a surge of oxygen uptake which was far greater than the requirements of any other phase of the activity. Many of the activities of the hospitalized patient show these fluctuations of effort. A patient getting out of and into bed without assistance may have a transient increase of his cardiac output

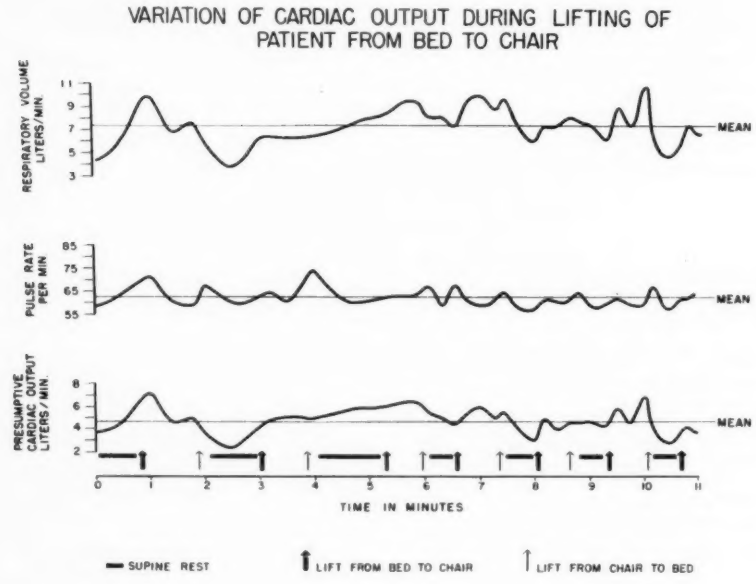
VARIATION OF CARDIAC OUTPUT DURING LIFTING OF PATIENT FROM BED TO CHAIR
RESPIRATORY VOLUME LITERS/MIN
PULSE RATE PER MIN
PRESUMPTIVE CARDIAC OUTPUT LITERS/MIN.
MEAN
TIME IN MINUTES
SUPINE REST
LIFT FROM BED TO CHAIR
LIFT FROM CHAIR TO BED

FIGURE 8. Response of the respiration, pulse and presumptive cardiac output of a normal subject to being lifted by three persons from a hospital bed to an easy chair and back. Arteriovenous oxygen difference determined at the end of 11 minute period. J. E. surface area 1.67 M².

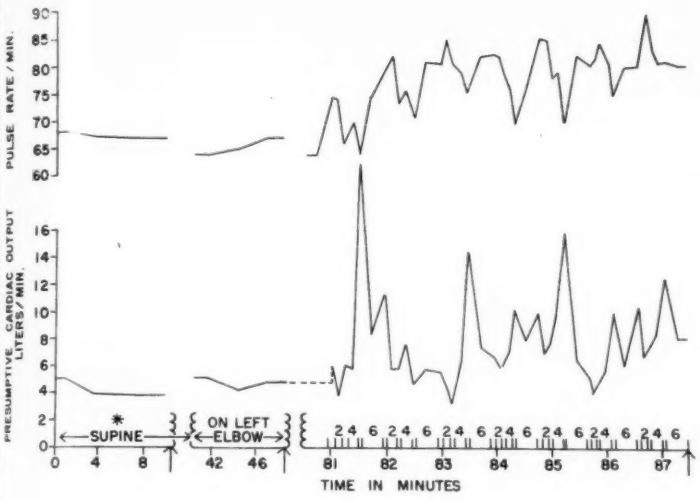

FIGURE 9. The variations of presumptive cardiac output and pulse rate during bed rest of a normal subject while reaching to a bedside table to pour and drink a glass of water. The vertical arrows below the baseline indicate the times at which the arteriovenous oxygen difference was estimated. Activity sequence indicated above the baseline:

1. Rolling onto left elbow and reaching to flask on bedside table.
2. Lifting flask and pouring water into glass.
3. Setting flask down and reaching for glass.
4. Raising glass to lips.
5. Setting glass on bedside table.
6. Lying down, supine.

M. R. surface area 1.86 M^2.

to 300 per cent of the basal level (figure 7). The effort required to sit up in bed unassisted from the supine position appears to be greater than any other phase of the act of getting out of bed. Yet this is an activity which is performed frequently by patients confined to bed. Getting up from an easy chair did not require as much cardiac work as did the act of sitting up in bed.

If a patient is lifted with care or assisted in getting out of and into bed the increases of cardiac output are not great (figure 8). To move the cardiac patient from the bed to a chair with minimal cardiac work, it is necessary that the patient relax and allow the assistants to perform the work of elevation. A careful explanation and care in execution can make the transfer from bed to chair and the return an activity of light effort.

Shifting and reaching in bed may also be activities stimulating cardiac work. To reach to the bedside stand for water, food, a book or other material may create a stress on the myocardium (figure 9). The strain of reaching or lifting at arm's length may cause transient swings of the cardiac output to 300 to 400 per cent of the output when at rest. Although these stresses are of short duration, they far exceed the stress produced by activities which the patient often is not allowed to perform.

Studies of fluctuations of cardiac output dur-

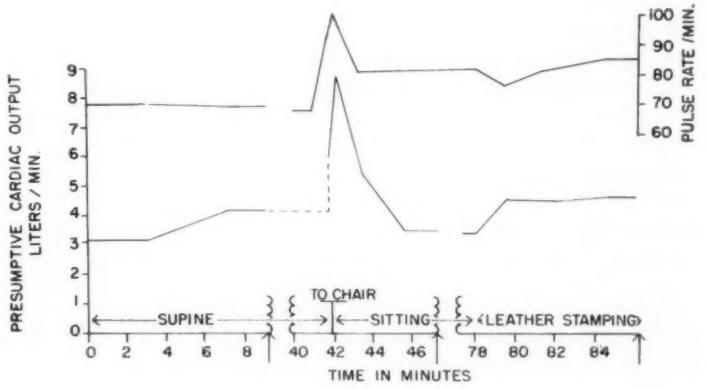

FIGURE 10. The effect of posture, movement and leather stamping on the presumptive cardiac output and pulse rate of a normal subject. Movement from bed to chair was as a patient might move without assistance. The vertical arrows below the baseline indicate the times at which the arteriovenous oxygen difference was measured. J. E. surface area 1.67 M^2.

ing activity requiring use of only the hands showed that aside from the high cardiac demand while moving from bed to chair without assistance there was only a slight increase due to hand activity (figure 10). In an experiment on leather stamping, the use of a mallet and stamping tool stimulated little increase in cardiac output. Chair activities or manual activities of this type create minimal load on the heart.

Discussion

The baseline of cardiac output used in this study has been that of a relaxed, resting, fasting individual lying supine in bed. The cardiac work under these conditions is near basal. If the individual sits quietly with support of head, trunk and extremities and with the feet and legs dependent, the cardiac output is slightly lower. This appears to be the condition of minimal cardiac work. Light activities involving use of the hands increase the cardiac output very little above this basal level. However, it should not be presumed that when a patient with cardiac disease is confined to bed his heart will have only this minimal work to perform. A cardiac patient will have emotional tensions unless heavily sedated. Any restlessness, moving or turning in bed will raise his cardiac output appreciably. Restriction of activity produces restlessness due both to boredom and to discomfort from being in bed continually. Instead of a basal cardiac output, the restless patient restricted to bed has an elevated cardiac output. Periods of diversional activity or periodic changes of position from bed to chair help to relax the patient and decrease stress on the heart.

The pulse rate cannot be considered an index of cardiac work if the posture is changed. During the change from recumbency to the upright position, with changes of the peripheral pooling of blood, the pulse rate changes reciprocally with the cardiac output while the arterial blood pressure remains practically constant.[18] Changes of pulse rate which occur during changes in activity and position are not reliable indexes of cardiac work.

The information available concerning the cardiac stress associated with various daily or occupational activities is meager. Much of our information must be obtained indirectly from the metabolic demands of various types of work. Assumptions made in estimating cardiac output during an activity, when only the oxygen consumption has been measured, may lead to sizable errors, but with our present knowledge this is the best judgment which can be made. In the trained athlete, cardiac output can increase for a short time to about nine times the basal rate; in the nonathlete, four to six times. Maximal oxygen intake varies between 10 and 14 times the basal oxygen consumption. Compared to this, Müller[19] found that the "endurance limit" of work—the upper limit of work which can be carried on by a normal individual continuously without an increasing accumulation of lactic acid or a rise of the body temperature—was 5 Calories (kilocalories) per minute or 500 per cent of the basal metabolism. This rate of work represents the maximum which can be carried on throughout the working day for months or years.

It would appear reasonable to rate the severity of activities in proportion to the greatest amount of work which the normal cardiovascular system can sustain for a prolonged period of time, i.e., the "endurance limit." A grade of cardiac stress based on the endurance limit is more meaningful when planning an activity program for a cardiac patient than is a grade based on transient maximal cardiac output. For normal healthy men, continuous activity requiring work beyond the endurance limit will exceed the capacity of the cardiovascular system, and deterioration will occur. When there has been myocardial or valvular damage, deterioration will occur when the cardiovascular stress is less than the normal endurance limit. The greater the damage, the lower must be the cardiovascular stress in order to avoid deteriorative changes. Conversely, when healing and repair take place, tolerance for cardiac stress will increase. The following levels of activity are based on the endurance limit of an adult of average size, 1.86 M.^{2} surface area:

1. Minimal activity—up to 1.5 Calories per minute, or 150 per cent of basal.

2. Light activity—up to 2.5 Calories per minute, or 250 per cent of basal.

3. Moderate activity—up to 3.5 Calories per minute, or 350 per cent of basal.

4. Heavy activity—up to 5.0 Calories per minute, or 500 per cent of basal, the endurance limit of Müller.

5. Severe activity—up to 7.0 Calories per minute, or 700 per cent of basal.

6. Excessively heavy activity—over 7.0 Calories per minute.

These grades would represent the following approximate changes of cardiac output, although it must be recognized that there may be considerable variation:

1. Minimal activity—up to 125 per cent of supine resting cardiac output.

2. Light activity—up to 200 per cent of supine resting cardiac output.

3. Moderate activity—up to 250 per cent of supine resting cardiac output.

4. Heavy activity—up to 300 per cent of supine resting cardiac output.

It is of interest to check the cardiac and energy requirements of common activities against these criteria. Vocational activities at a desk or bench which do not involve reaching or lifting are light activities. Walking at a moderate speed, 2.5 mph, is at the lower level of moderate activity. Although dressing, undressing and washing are variously reported as falling in the moderate activity range (200 to 350 per cent of basal oxygen consumption) patients often are allowed to carry out these activities early in recovery. Showering has been found to be a heavy activity (340 to 477 per cent of basal oxygen consumption).[12] Stair climbing is the most strenuous activity indulged in by most people. At the normal rate, stair climbing is an excessively heavy activity.[15] Even when cardiac patients are advised to climb stairs slowly, at the rate of 15 steps per minute, this constitutes a heavy activity. These activities by the patient with myocardial damage frequently are tolerated because it is difficult for the patient to live at home without performing them, yet much less stressful activities are prohibited long after they might be performed with safety.

Emotional tension is one of the major stresses which is difficult to control for the patient with acute myocardial disease. Anxiety is a powerful stimulant to increase cardiac work.[20] The cardiac patient is removed from family, social and job contacts, put to bed in a hospital, restricted in activity, and told to relax. He may be in pain. He certainly has many anxieties. He cannot escape concern over immediate and future problems. If he has no diversion he has no escape from worries about his present or future. Confinement to bed supports his worst fears about the seriousness of his condition and about his imminent death. Permission to sit in a chair provides psychologic reassurance to the cardiac patient that his condition is not hopeless. Light handicrafts provide diversion so that he will relax. The periodic shift from the bed to an armchair changes the patient's position and relieves the stiffness and discomfort resulting from a long stay in bed. Emotional tension is decreased and, with it, cardiac work.

The patient with heart disease who is not able to increase his cardiac output with increasing activity, as the normal person does, accumulates lactic acid and builds up an oxygen debt. In the postexercise period the heart rate and cardiac output remain elevated until this oxygen debt is corrected. The level of activity at which the oxygen debt begins to accumulate and the time required after work to correct the oxygen debt accumulated during the work are indexes of the functional capacity of the heart. The activities studied here, varying from minimal to moderate in cardiac stress, might be used to test the working capacity of the damaged heart. The determination of the oxygen debt or the pulse rate recovery time following one of these activities for which the cardiac output is known would provide an objective measure of cardiac ability. The different grades of cardiac output required by these activities make it possible to follow the improvement of cardiac reserve from minimal to moderate or high levels of cardiac output.

Summary

The effects of various hospital activities on the cardiac output have been studied using

the acetylene method for estimating arteriovenous oxygen difference. The lowest levels of cardiac output were obtained when subjects sat quietly, well supported in an arm chair. Pooling of blood in the feet and legs is an important factor in the lower cardiac output when sitting than when supine. Activities requiring use of only the hands increase cardiac output very little. Activities requiring arm support or effort for shifting or balance of the trunk require a greater cardiac output. The greatest cardiac stress occurs when the body is lifted. A classification of the relative cardiac stress produced by the various activities is suggested, based on the endurance limit of the normal cardiovascular system.

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Shock—With Particular Reference to Endotoxin Shock

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IN considering the mechanism of shock, it is important to go back to primary principles. Shock may properly be defined as a state of persistent and progressive arterial hypotension of a degree sufficient to impair the function of organs such as the kidney, liver and brain to the point of death; it is not ordinarily reversible spontaneously and may be irreversible in spite of therapy. This definition reserves the term "shock" to those hypotensive states from which spontaneous recovery usually does not occur, implying that in shock a process or processes have been set in motion which are progressive in the direction of deterioration.

Shock is functionally a circulatory phenomenon, but it would be a mistake to assume a priori that it is necessarily limited to the vascular system in its mechanism. Nervous, endocrine and other metabolic processes may be involved in its progression. Nevertheless, the prime defect in shock is a low perfusion rate of vital organs. The reasons for the perpetuation of the low perfusion rate are the essential problems in shock.

The perfusion rate of any organ depends on three, and only three, factors: (1) the head of pressure, (2) the number and bore of the open blood vessels, and (3) the viscosity of the blood. Thus, in attempting to account for shock, one must find a process or processes which influence one or more of these three factors. Further, one must account for the tendencies toward progression and irreversibility of the total process.

In the circulatory system as a whole, the head of pressure for perfusion of various organs again depends on three quantities: (1) cardiac output per unit time, (2) mean resistance to runoff from the arterial to the venous bed, and (3) viscosity of the blood. For the most part, blood viscosity changes relatively little, and we probably can eliminate it from consideration in connection with the

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primary causes of shock. This leaves what would appear to be a rather straightforward problem in hemodynamics in analyzing the causes of shock. In the central position is perfusion pressure, which is itself determined by cardiac output and mean flow resistance from the entire arterial tree and the specific flow resistance through cortical organs whose perfusion rate is crucial to life.

Several interdependent relations complicate the situation, however. First, cardiac output depends on the rate of return of blood to the heart, which depends on the volume of the total vascular bed, which itself controls resistance to flow from arteries to veins. For example, let us assume that normally 40 per cent of the blood in the body is in the veins and that this occurs when the venomotor tone is such that the pressure gradient for filling the heart is normal, say, 5 mm. Hg from great veins to right atrium. Let us now suppose that the venomotor tone changes so that 45 per cent of the blood is in the veins and the gradient falls to 3 mm. Hg. Obviously, less blood will flow from veins to heart (if the bore of the channel from the great veins to the atrium is not increased) and, since cardiac filling declines, cardiac output will also fall.

On the arterial side, a decrease in resistance to flow through the blood vessels in one organ will tend to increase the perfusion of that organ, but the very increase in flow will produce a fall in the perfusion pressure. If resistance in all organs changes in proportionate amounts, there will not be an increase in perfusion of any of them, so long as cardiac output is unchanged.

It is possible to have a damaging decline in perfusion rate to certain vital organs without a universal decline in perfusion rate to all organs. This can occur if there is selective vasoconstriction in some organs and not in others, even at normal arterial blood pressures. This, in fact, appears to occur in the kidney after administration of endotoxin.

Normally, a barostat mechanism regulates blood pressure. Nerve endings in the carotid sinus and in the arch of the aorta are stimulated by stretching and set up nerve impulses which travel to the central nervous system, particularly to reflex centers in the medulla and hypothalamus where vasomotor centers are located. These nerve impulses are depressor in character. That is, when they increase in frequency the vasomotor centers are depressed, in the sense that fewer vasoconstrictor impulses are sent out and vasodilation results, inducing a fall in blood pressure. With the fall in blood pressure, the distention of the aorta and the carotid sinus diminishes and the stretch-sensitive endings discharge less frequently. Thus the vasomotor center is relieved of its depressor influences and can resume its vasoconstrictor activity. So the cycle can start over again. This type of regulator is like a governor on a steam engine. The "set" of the vasomotor center can be altered, just as the setting of the engine governor can be, thus determining the level at which constrictor impulses increase or decrease and thereby regulating the mean pressure level.

In shock, it is conceivable that the defect or defects in the perfusion-regulating functions of the body could be situated in one or more locations in the total regulating apparatus. Although much is known about the pathogenesis of shock, many key problems remain unsolved and one must consider the problem in its entirety to avoid serious error.

Table 1 is a schematization of factors operating, or possibly operating, in the development of shock. Cardiac output is listed first because in all shock states this quantity ultimately falls, and therefore it can be said that all other mechanisms ultimately operate to bring this about. The failure of cardiac output is not ordinarily due to failure of heart muscle, however, except in the so-called shock after severe myocardial infarction. The latter must be looked on somewhat differently from other forms of shock, although it is possible that the progressiveness of the hypotension in this situation depends on factors similar to those acting in other forms of shock.

The purest situation in which lowered cardiac output can be considered the primary factor in shock is after massive bleeding (IA3 in the table). Even after hemorrhage, however, one cannot account for shock simply on the basis of loss of blood volume; even after

TABLE 1

SCHEMATIZATION OF FACTORS OPERATIVE IN PATHOGENESIS OF SHOCK

BLOOD PRESSURE DETERMINANTS	CHANGES PROMOTING HYPOTENSION
I. Cardiac output	Fall
A. Cardiac filling	Fall
1. Venomotor tone	Fall
2. Trapping of blood	Increase
a. Hepatic	Increase
b. Mesenteric	Increase
c. Pulmonary	Increase
3. Blood volume	Decrease
B. Cardiac ejection	Fall
1. Myocardial failure	Progression
2. Cardiotonic influence of epinephrine, etc.	Decrease
3. Heart rate	Fall
II. Over-all resistance to systemic blood flow	Fall
A. Barostat mechanism	
1. Sensitivity of stretch receptors	Increase
2. "Set" of central mechanism	Lowering
3. Chemical effects of changing pO_2, pCO_2, pH, etc.	?
4. Effects of other chemical agents	?
B. Humoral factors operating generally	
1. Output of vasodilator substances	Increase
2. Output of vasoconstrictor substances	Decrease
3. Changing pH	Lowering
4. Changes in sensitivity to vasoconstrictors	Decrease
III. Indirect mechanisms	
A. Adrenal cortex	Deficiency
B. Adrenal medulla	Deficiency
C. Renal ischemia	(See text)
D. Hepatic ischemia	(See text)
E. Liberation of vasoactive substances from blood constituents	(See text)

full replacement, recovery need not and often does not occur. Thus, although the loss of blood volume is primary, secondary sequelae account for the progressive irreversibility of the condition. In essence, therefore, the knotty problem in research on shock is to identify the intermediate mechanisms. They need not be the same in all forms of shock, but it has not been demonstrated that all forms do not have some ultimate "final common path." In fact, to me it would seem likely that many roads might lead to a "final common path" of precipitate deterioration, so steep that reversal is impossible with our present knowledge (or rather ignorance) of the chemical processes occurring in ischemic organs.

It is common knowledge that the likelihood of recovery after hemorrhagic hypotension diminishes as the duration of the low blood pressure increases. It would seem that certain (unknown) chemical reactions must progress to a critical stage in some ischemic organs before irreversibility occurs. Apparently this stage is different in various organs, and it may be different in various species of animal. Lillehei[1] and associates showed that in the dog the intestine is probably the most critical organ in hemorrhagic shock, although it is by no means excluded that changes in the liver are not essential to the syndrome. Further, one must be extremely cautious in extrapolation from one species to another. This is illustrated in a dramatic way in connection with endotoxin shock.

When gram-negative endotoxin (from *Escherichia coli*, for example) is administered to a dog in massive doses (1 to 10 mg. of killed cells per kilogram), there is a prompt large fall in blood pressure. This is associated with an equally prompt and comparably large rise in portal venous pressure, as Weil and associates[2] have found. There is also a prompt rise in the weight of the liver, with a slower rise in intestinal weight.[3] Moreover, if by suitable means[4] one maintains cardiac inflow constant, using an external reservoir into which all venous blood flows and from which blood is pumped at a constant rate into the right side of the heart, one finds that endotoxin produces virtually no immediate fall in arterial blood pressure. Thus it can be concluded safely that the initial "shock" reaction to endotoxin in the dog is due to diminished cardiac output caused in turn by trapping of blood in the hepatic and portal beds.

In the cat, too, a large drop in arterial pressure may follow the administration of massive doses of endotoxin. However, Kuida and coworkers[5] found that although the portal pressure increases slightly the rise is not great, and the rise in weight of the liver seen in the dog is virtually absent. There may be a very large rise in pulmonary arterial pressure. Kuida and associates[5] also found that a concomitant rise in the weight of the lung occurs due to pooling of blood upstream from the pulmonary small veins, which are constricted. Thus, in the cat, the pulmonary small veins play the role that hepatic small veins do in the dog. The cat's hepatic veins are not totally insensitive to the agents in question, but they are less so than the dog's, and therefore an entirely different vascular bed serves the trapping function after endotoxin. The Macaca rhesus monkey reacts to administration of endotoxin more like the cat than like the dog. It is unknown how the human subject reacts.

To return to the analysis in table 1, it will be seen that the initial hypotensive episode is due to the operation of factor IA2a in the dog and IA2c in the cat.

However, these are not the only factors involved in endotoxin shock. The work of Hinshaw[6] and associates gives critical proof of this. These investigators proved that the eviscerated dog is susceptible to endotoxin shock. To be sure, there is no immediate fall in blood pressure after administration of endotoxin, because the initial large pooling of blood in the liver and intestines is obviated. However, after one or more hours the arterial blood pressure begins to fall, and fatal shock occurs long before the control animals, subjected to evisceration alone, die. Further, arterial blood pressure falls even when cardiac output is kept constant by the controlled-inflow technic. Thus one can say positively that endotoxin induces a fall in "total peripheral resistance" in such animals.

To revert again to the table, it will be seen that factor II is implicated in endotoxin shock. Vick,[7] attempting to analyze this mechanism further, studied the responses of isolated blood vessels to the blood circulating in the dog after administration of endotoxin. It appears that there is a biphasic response as to circulating vasoactive agents. The first response is a contraction of smooth muscle, and the second, and more prolonged, action is a relaxation. These results seem to show that at least two substances appear in the blood, one a vasoconstrictor and the other a vasodilator. It may be that both are liberated simultaneously and that their relative proportions change, or that the vasodilator only appears later in the period of endotoxin action. Thus it appears that both processes IIB1 and IIB2 are operative, with the latter moving in a direction opposite to that favoring hypotension and the former changing in the expected direction to promote shock.

Hinshaw and associates,[8] in further studies, showed that the blood-perfused isolated lung responds to endotoxin by vasoconstriction. This response is absent when dextran-Ringer is used for perfusion, as it is when homologous plasma free of leukocytes and thrombocytes is employed. Readdition of the "buffy coat" to such cell-free plasma restores its ability to serve as an adequate substrate for endotoxin action. One can deduce from these studies that at least one vasoconstrictor substance liberated by endotoxin depends on the presence of platelets or white blood cells, or both,

for its liberation. It is likely that endotoxin produces or liberates the vasoconstrictor substance or substances from the platelets or cells. Thus the schematic mechanism IIIE appears to be operative. Among plausible substances possibly contributing to the effect are histamine and 5-hydroxytryptamine, but they have not been identified positively. It is possible, too, that liberation of epinephrine may enter the total picture, because when the blood pressure of the dog falls after administration of endotoxin, the blood of the animal causes profound vasoconstriction when it is used to perfuse an isolated limb.

The most positive conclusion one can make from a study of shock produced by endotoxin is that no single mechanism is responsible for the syndrome in its entirety. One is forced to conclude that several different processes come into play and that they may be quite different in various species of animal. There may be a "final common path" for shock, but it has not yet been demonstrated. If there is one, it seems possible that it is a vasodilator substance liberated by such an organ as the liver after exposure for a protracted period to damaging ischemia.

Another distinct possibility in regard to the mechanism of a "final common path" would be an effect on the "set" of the barostat. A chemical agent that would lower the pressure at which vasoconstrictor volleys would fire from the vasomotor center could obviously perpetuate hypotension. In terms of table 1, this would mean operation of the schematic mechanism IIA4.

The kidney is seriously damaged by prolonged hypotension and especially by endotoxin. Hinshaw[9] has shown that, in the eviscerated dog, administration of endotoxin is followed by a loss in renal weight which may be as great as 25 per cent. This could only result from severe vasoconstriction. That the partially ischemic kidney can liberate an enzyme, renin, capable of producing a vasoconstrictor substance, hypertensin, is well known. Whether it can produce other substances is not known. However, we cannot ignore the possibility that renin or some other active agent liberated by the kidney participates indirectly or directly in the shock mechanism.

I have outlined the fundamental physiologic considerations involved in the solution of the problem of shock. I have not attempted to review the literature on the problem; rather, I have indicated the unsolved questions. The complexity of the problem has been stressed, partly because it has so frequently been oversimplified, even by investigators. The practicing physician may properly console himself in his frustration over management of shock with the knowledge that the investigators of the problem are themselves in the dark about the real cause of irreversibility. Until some schema like table 1 can be drawn without important gaps in our knowledge and without uncertainties as to which factors play major roles, the problem will be a partial enigma.

In the meantime, the physician must be most concerned about restorative measures before the stage of probable irreversibility is reached. This means restoration of blood volume as soon as possible after hemorrhage or after loss of plasma. It means attention to replacement therapy in adrenocortical insufficiency after trauma or hemorrhage. It means vasomotor support when there is loss of vasoconstrictor tone, although in this situation he must weigh the hazard of injury by vasoactive agents in high dosage.

In another few years it is to be hoped that the important missing information may be obtained. Then it may be possible to reverse in many instances what is now irreversible shock.

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Dysproteinemia

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MANY disease states are associated with abnormalities of the blood serum proteins. Whenever synthesis or metabolism of one or several of the blood plasma proteins is primarily or fundamentally disturbed, we speak of a dysproteinemia. Dysproteinemia may be evidenced by either a deficiency or an excess of a protein fraction in the serum. Newly described clinical entities affirm that dysproteinemias are not as rare as formerly supposed. The list has grown in the past decade and probably still is not complete.

HORACE H. ZINNEMAN

It may be expedient for this discussion to separate the dysproteinemias into two groups: (1) one characterized by absence or marked diminution of one or more normal protein fractions in the blood serum, and (2) one in which abnormal proteins (paraproteins) appear in the blood serum.

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Deficiency of Normal Protein Fractions

The gamma globulin fraction of the blood serum is decreased in various diseases. In the nephrotic syndrome, for instance, there is a characteristic decrease of albumin and gamma globulin, coupled with rising alpha$_2$ and beta globulins. Similarly, the serum of patients with dystrophia myotonica may have a low gamma globulin fraction.[1,2] However, these changes in the serum proteins do not represent the basic disturbances, and neither of these diseases should be considered dysproteinemias.

The relative quantity of gamma globulin in the serum of newborn infants is about the same as in the serum of their mothers. During the first month of life, the level of gamma globulin drops to about one-third of the initial level. It remains at that level for about three months and then gradually rises until it reaches adult levels at the age of two years.[3] Hypogammaglobulinemia, then, is a physiologic state during the first two years of life.

Agammaglobulinemia represents a far more

serious depletion of gamma globulin, and apparently is not reversible. The condition was first reported as a congenital sex-linked defect observed in male children.[4-6] Gamma globulin is absent or nearly absent from the blood serum (figure 1), and there is an associated absence of circulating humoral antibodies to bacteria. These children have multiple recurrent infections such as pneumonia, meningitis, otitis media, sinusitis and conjunctivitis. The problem of recurrent infections became apparent only as a consequence of antibiotic therapy: prior to the advent of antibiotics, the patients succumbed at an early age.

The first case of agammaglobulinemia in an adult was reported in 1953.[7] By 1954, the differences between the disease in children and that in adults were sufficiently clear to designate the adult form as "acquired agammaglobulinemia."[8,9] Patients with this form of the disease usually had a normal childhood and adolescence. Later, during adult life, the disease developed, sometimes without known cause but more often following a disease process involving the lymphatic system such as lymphatic hyperplasia,[10-12] histoplasmosis,[13] tuberculosis,[14-16] Hodgkin's disease or lymphatic leukemia,[10,17] sarcoidosis[8,9,18] or thymoma.[19-21] Steatorrhea has been a surprisingly frequent complication.[16]

Acquired agammaglobulinemia is not confined to males. In both the congenital and acquired forms, the deficiency is based on failure to synthesize gamma globulin rather than on an excessive catabolism of this protein fraction.[6,16,22] Plasma cells are characteristically absent from the bone marrow or lymphatic tissues.[22] Patients with congenital or acquired agammaglobulinemia reportedly have little resistance to bacterial infections but usually have normal resistance to viral diseases. Although the deficiency in humoral antibodies can be demonstrated by stimulation with a variety of bacterial antigens,[6,9,22] the recurrent infections are most often caused by pneumococci. Recurrent infections with gram-negative organisms or micrococci have not been a frequent problem in patients with agammaglobulinemia, and their resistance to infection with *Mycobacterium tuberculosis* does not seem

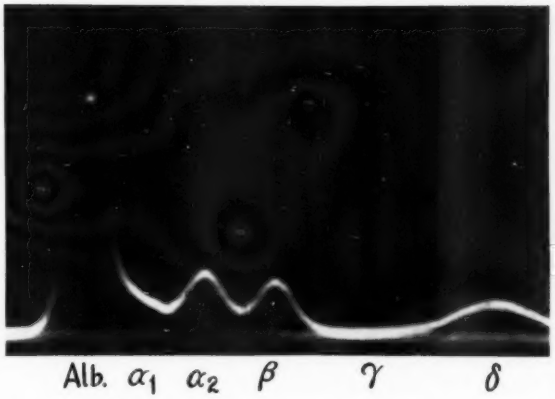

FIGURE 1. Electrophoretic pattern (Tiselius) of the blood serum of a patient with acquired agammaglobulinemia. Gamma globulin is absent. (The delta peak is an artefact inherent to the method, caused by a diffusion gradient.)

to be impaired.[14,16,23] In this connection, it is intriguing to remember that treatment of pneumococcal pneumonia with type-specific hyperimmune serum brought about a decrease of fatalities in this disease, whereas hyperimmune serums often were clinically ineffective against bacteria other than pneumococci. The absence of gamma globulin does not decrease delayed bacterial hypersensitivity as a result of infection. A patient with agammaglobulinemia will have a positive reaction to a skin test on infection with *Myco. tuberculosis* or BCG vaccine given for the purpose of active immunization.[14,16,23-25]

Good and Varco[26,27] were the first to carry out successful homotransplants of skin from unrelated donors to patients with agammaglobulinemia; they concluded that the failure to reject homografts was caused by an absence of host antibodies. Recent studies suggest not only a deficiency in gamma globulin but also an associated defect in at least two subfractions of beta globulin in the agammaglobulinemia.[28]

Prophylactic replacement therapy consisting of intramuscular administration of pooled human gamma globulin appears to have been successful in preventing bacterial infections in children with congenital agammaglobulinemia.[5,6] In the acquired form of the disease,

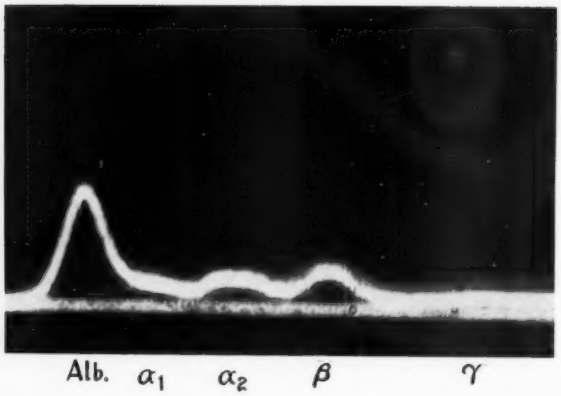

FIGURE 2. Electrophoretic pattern (Tiselius) of the blood serum of a patient with idiopathic hypoproteinemia. Note the marked depletion of albumin and gamma globulin.

this therapy often has failed to afford such protection.[9, 10, 13, 14, 19, 25] For the latter patients, prophylactic penicillin or a combination of this antibiotic with gamma globulin has been satisfactory. At present, I am observing the oldest known surviving persons with congenital agammaglobulinemia, two brothers aged 16 and 22 years. They have survived innumerable bouts of pneumonia, sinusitis, otitis media and other infections because of prompt therapy of each new infection with antibiotics or sulfonamides.[16]

One instance of apparent *absence of beta globulin* from human serum was reported recently.[29] Since the iron-binding protein fraction is contained within beta globulin, one would expect such a person to have severe iron-deficiency anemia, which indeed the patient did have. Iron medication did not influence the anemia, and blood transfusions afforded only transient benefit.

In some cases of multiple myeloma, deficiency of gamma globulin may be the only abnormality of serum protein.

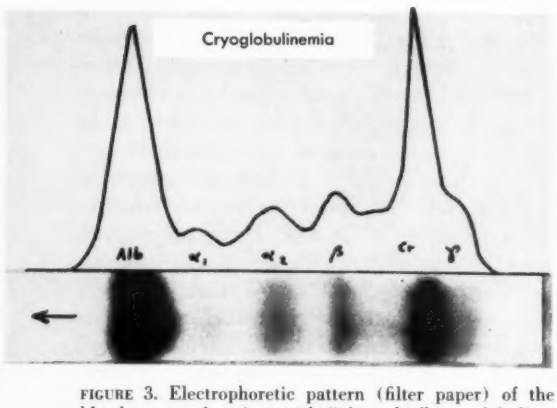

FIGURE 3. Electrophoretic pattern (filter paper) of the blood serum of patient with "idiopathic" cryoglobulinemia. The abnormal protein precipitated at 35.5° C., and in the electrophoretic pattern it appeared within the "fast" gamma range (Cr). A Tiselius pattern could not be obtained because the procedure is performed at a temperature of 2° C. Electrophoretic study by means of filter paper was feasible only when the entire apparatus was placed in a walk-in incubator.

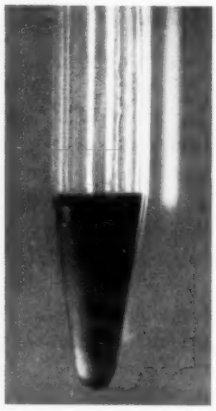

FIGURE 4. Same case as represented in figure 3. A gel formed by coprecipitation of cryoglobulin with normal blood proteins takes up 80 per cent of the entire volume of the serum and is seen as a semiopaque substance. Supernate represents 20 per cent of the volume and consists of normal serum.

FIGURE 5. Skin of patient with "idiopathic" cryoglobulinemia represented in figures 3 and 4. Purplish blotches appeared at room temperature and faded when the patient was placed in an incubator at 37° C.

Idiopathic hypoproteinemia is a rather rare condition affecting adolescents or young adults, characterized by edema, low serum proteins, absence of proteinuria, and a tendency to recurrent pneumococcal infections.[30-32] The electrophoretic pattern of the serum is characteristic, revealing marked depletion of albumin and gamma globulin and less involvement of the alpha and beta globulins (figure 2). Nitrogen balance was negative in one case,[33] while in others it reportedly was positive.[30,31] There is no known effective therapy for idiopathic hypoproteinemia. Spontaneous remission may occur.

Paraproteinemias

The paraproteinemias are characterized by the presence of an abnormal protein in the serum. This abnormal protein may have the electrophoretic mobility of gamma, beta or alpha globulin but differs from these normal globulins physically, chemically and immunochemically. In the electrophoretic pattern, the abnormal proteins appear as sharp, slender peaks which indicate homogeneity. Cryoglobulinemia, pyroglobulinemia and macroglobulinemia often are associated with various underlying primary diseases, whereas multiple myeloma always seems to be a specific disease.

Cryoglobulinemia was first described by Lerner and Watson[34,35] in 1947. The blood serum contains an abnormal protein which usually migrates within the range of gamma globulin (figure 3) and which precipitates at temperatures below 37° C. (figure 4). The precipitation is reversible by heating to 37° C. or above.[36] The appearance of clinical symptoms depends on the temperature at which precipitation occurs and the quantity of cryoglobulin in the serum. It has been shown that cryoglobulin precipitate contains cholesterol esters and phospholipids.[37,38] If the temperature of precipitation is 35 to 36° C., it may occur within the superficial blood vessels, producing the clinical picture of cold intolerance, painful petechiae or red skin blotches (figure 5), Raynaud's syndrome,[39] or arthralgia on exposure to cool temperatures. Gangrene of the digits,[40] cerebral purpura and retinal hemorrhages also may occur as a consequence of precipitation of cryoglobulin in small blood vessels.[41] Occasionally a cryoglobulin may also have the properties of a macroglobulin.[42-45] In most cases, cryoglobulinemia is associated with a primary disease such as multiple myeloma,[46-49] carcinoma,[35] lymphoblastoma,[39,50-52] collagen diseases,[53] subacute bacterial endocarditis,[35] or other chronic infection.[54]

One may suspect the presence of cryoglobulinemia whenever a "coagulation" or jelling of withdrawn blood within the needle or syringe renders venipuncture difficult or impossible. Use of a preheated syringe and needle will allow easy withdrawal. The blood must then be allowed to clot at 37° C. Otherwise, most or all of the cryoglobulin will become enmeshed within the blood clot and lost to detection in the serum. Fallacious values would also be obtained for the hematocrit and all chemical determinations of the serum.

Pyroglobulinemia is a condition in which the blood serum contains a protein that coagulates at about 55° C. It usually is detected in the serologic laboratory when the serum is placed in a water bath at 56° C. for the purpose of complement inactivation. The serum forms a solid coagulum that is not reversible (figure 6). Pyroglobulinemia as a rule is associated with either multiple myeloma or lymphoblastoma.[55,56]

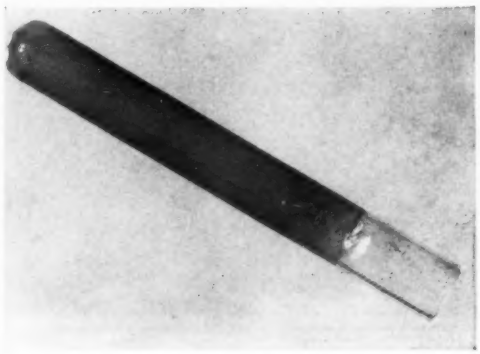

FIGURE 6. Serum of a patient with multiple myeloma which coagulated irreversibly in a water bath at 56° C. where it had been placed for inactivation of complement. This myeloma paraprotein was also a pyroglobulin. In the electrophoretic pattern, it appeared within the range of beta globulin (see figure 12).

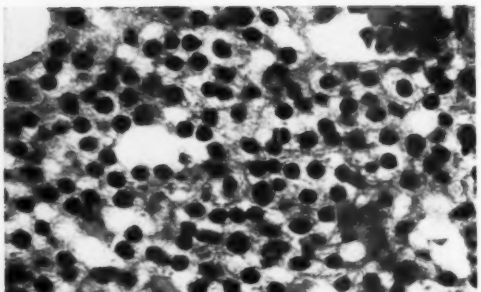

FIGURE 7. Invasion of the bone marrow with lymphocytoid cells in macroglobulinemia.

Macroglobulinemia (Waldenström's disease) was first described in 1944.[57] It affects older men. The patients complain of weakness, loss of weight, fatigue, fever and sometimes urticaria. Large amounts of macroglobulin in the blood may result in increased viscosity and intravascular stasis, leading to petechiae, ecchymosis, purpura, retinal hemorrhages, sudden blindness, epistaxis, bleeding gums, gastrointestinal bleeding, cerebrovascular accidents, Raynaud's phenomenon, and chronic leg ulcers.[42, 43, 45, 58-65] Splenomegaly, generalized lymphadenopathy and a refractory normochromic normocytic anemia usually are present. Uniform infiltration with lymphocytoid cells obliterates the histologic structure of the enlarged lymph nodes, making them indistinguishable from lymph nodes found in lymphosarcoma. The peripheral blood always shows rouleaux, and often shows neutropenia and thrombopenia. The bone marrow is hypocellular, and attempts at biopsy of the bone marrow may be repeatedly unsuccessful. The typical histologic picture consists of invasion of the bone marrow by small lymphocytoid cells (figure 7).[43, 45, 57, 59, 60, 61, 64, 66, 67] Plasma cells may be present[45, 60] or increased.[59, 67] On the electrophoretic pattern, a macroglobulin appears as a sharp, homogeneous peak (figure 8) and migrates at the mobility of gamma or beta globulin. This appearance makes it indistinguishable electrophoretically from the paraprotein peaks of multiple myeloma. Ultra-

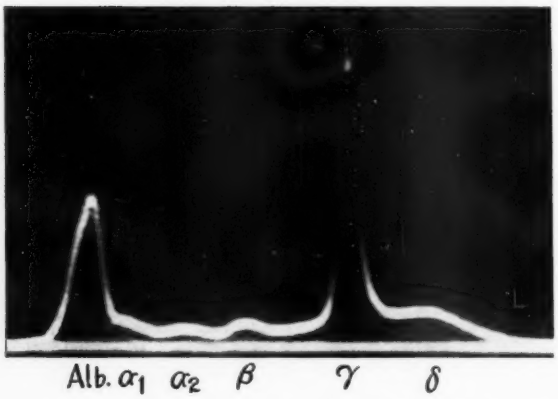

FIGURE 8. Electrophoretic pattern (Tiselius) of the blood serum of a patient with macroglobulinemia. The slender, abnormal macroglobulin peak migrates within the range of gamma globulin. Note the concomitant decrease of normal globulins and albumin.

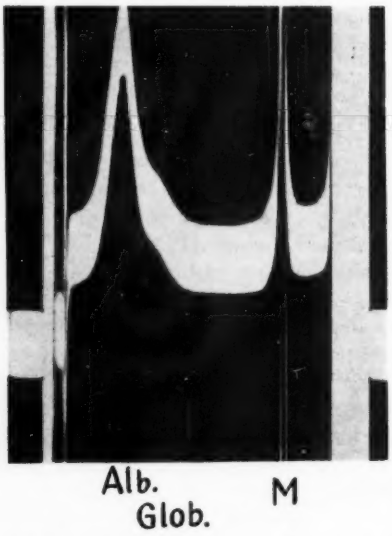

FIGURE 9. Ultracentrifugal pattern in a case of macroglobulinemia showing a peak of albumin, the normal globulins appearing as a shoulder on the descending limb of this peak. The much heavier molecules of the macroglobulin (M) can be seen as a separate peak to the right.

centrifugation, however, defines macroglobulins and shows them to be much larger and heavier than the molecules of the paraproteins of the ordinary multiple myeloma (figure 9).

The sedimentation constant of a macroglobulin is between 16 and 20 Svedberg units. This corresponds to a molecular weight of about 1,000,000, compared with the molecular weight of normal gamma globulin of 160,000.[57, 60, 65, 66] There is evidence that the macroglobulins are polymers of a protein molecule of the same weight as normal gamma globulin and that the cross linkage involved in formation of the polymer is of the nature of a sulfur-sulfur (cystine) bond. The usual macroglobulin molecule contains about six monomers of the size of normal gamma globulin molecules.[67, 68]

Macroglobulinemia may be "idiopathic" or found in association with malignant neoplasm,[59, 63, 65] multiple myeloma,[59, 66] cirrhosis,[43] disseminated lupus erythematosus,[69] Sjögren's syndrome[70] or congenital syphilis.[71] Treatment of macroglobulinemia is largely empirical but should be directed at reducing the macroglobulins in the blood serum to prevent disastrous intravascular stasis. Since macroglobulins probably originate in the reticuloendothelial system of the lymphatic organs, one of our patients was treated with a combination of deep x-ray therapy, nitrogen mustard and prednisone. The results have been very gratifying thus far, over one year.[67]

Multiple myeloma is probably the most fascinating and best known of the paraproteinemias. The plasma cells of the bone marrow are increased in number and immature in appearance. Since normal plasma cells produce gamma globulin,[72, 73] it is not surprising that the product of abnormal plasma cells should also be abnormal.

A recent study[74] described a transmissible plasma cell tumor in mice which resembles human myeloma. Osteolytic bone lesions occur, and the blood serum of the affected animals contains a paraprotein that resembles very closely the paraprotein of human multiple myeloma. Saline extracts of the tumor cells contained the paraprotein in nearly pure form.

Lane[75] reported a case in which surgical removal of a single plasmocytoma from a human mandible resulted in the return of abnormally elevated serum globulins to normal levels.

The paraproteins of multiple myeloma may migrate with the electrophoretic mobility of gamma, beta or even alpha$_2$ globulins, but chemically they are related to gamma globulin.[76] In the electrophoretic pattern, they appear as sharp, homogeneous peaks unlike those of the normal globulins. They seem to exist at the expense of normal serum proteins. Serum albumin always is decreased, and gamma globulin is decreased or absent in the presence of paraproteins. Once an abnormal peak appears in the electrophoretic pattern of the serum of a patient with multiple myeloma, the pattern remains relatively unchanged.

Quantitative measurements by chemical fractionation are in close agreement with electrophoretic values in normal human serums but not in those containing the paraproteins of multiple myeloma. In the paraproteins, chemical fractionation results in smaller values.[77, 78] The differences between normal gamma globulin and myeloma paraproteins have also been demonstrated by immunochemical methods.[79-81] Some of the paraproteins of multiple myeloma are anticomplementary and responsible for a biologic false-positive Wassermann reaction.[69, 78, 82] Others may have the properties of cryoglobulins, pyroglobulins or macroglobulins.

Bence Jones proteins are the least closely related to gamma globulin. Their molecular size is small enough (24,000 to 80,000)[83-85] to pass the normal glomerular filter and thus they may appear in the urine. Amyloid deposits probably represent the precipitation of an abnormal protein[86] and are found in about 10 per cent of all cases of multiple myeloma.[87] Amyloid is deposited in a distribution characteristic of primary amyloid (paramyloid), namely, in the mesenchymal tissues, particularly the walls of the blood vessels, heart muscle, tongue, and smooth muscles of the gastrointestinal tract.[87, 88] Amyloid deposits around major joints may give them an appearance and limitation of motion similar to that seen in rheumatoid arthritis.[89]

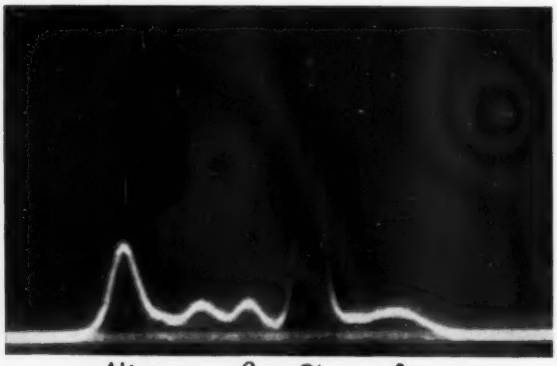

FIGURE 10. Electrophoretic pattern (Tiselius) of the serum of a patient with multiple myeloma. The paraprotein is seen as a high, slender peak in the range of gamma globulin.

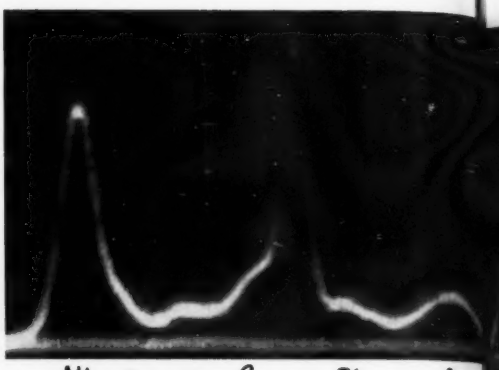

FIGURE 11. Electrophoretic pattern (Tiselius) of the serum of a patient with multiple myeloma. The paraprotein is of the "M" type and migrates between beta and gamma globulins.

For convenience, multiple myeloma may be divided into five types in accordance with the electrophoretic mobility of the abnormal protein peak:

1. Gamma type. The paraprotein peak in the serum travels in the area of normal gamma globulin (figure 10). One may distinguish between "slow" and "fast" gamma types. The gamma type of multiple myeloma represents about 60 per cent of all cases and usually is associated with myeloma cells of large diameter in the bone marrow.[90] The urine may or may not contain Bence Jones proteins. Recurrent pneumococcal pneumonia is a rather common complication. These patients, similar to those with agammaglobulinemia, are unable to respond to challenges from bacterial antigens with circulating antibodies.[91,92] In fact, a deficiency of normal gamma globulin actually exists. The large "gamma globulin" peak in the serum electrophoretic pattern represents an abnormal paraprotein that is immunologically inert.

2. M type. From 10 to 15 per cent of all serum electrophoretic patterns of multiple myeloma have an abnormal protein peak in the area between the gamma and beta peaks (figure 11). The same properties and clinical characteristics apply in this type as in the gamma type.

3. Beta type. About 10 per cent of all myelomas fall in this category. The paraprotein peak migrates with the electrophoretic mobility of beta globulin (figures 12 and 13). The clinical course usually is shorter and more fulminating.[87] The myeloma cells of the bone marrow usually are small.[69,90] Recurrent pneumococcal pneumonia may occur in cases of "beta myeloma" in which the normal gamma globulin peak is diminutive or absent.

4. Alpha type. An extremely fulminating

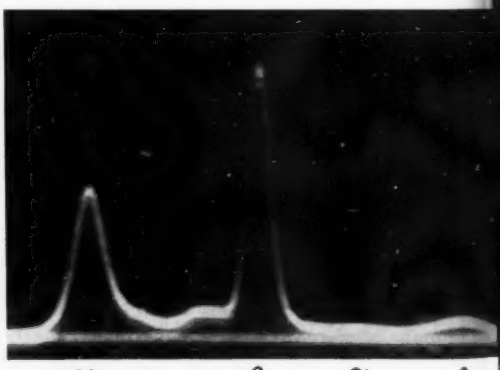

FIGURE 12. Electrophoretic pattern (Tiselius) of the serum of a patient with multiple myeloma. The paraprotein, which also has the quality of a pyroglobulin, migrates with beta globulin. Note the decrease of normal protein fractions, particularly gamma globulin.

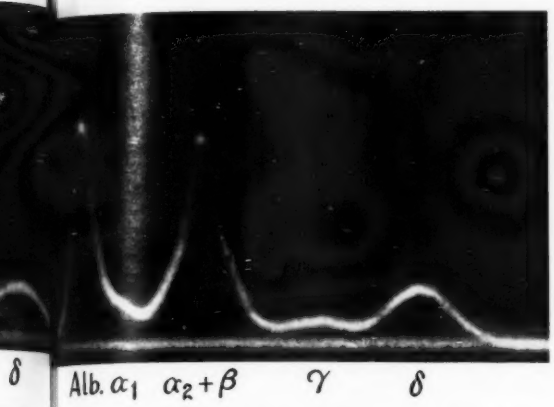

FIGURE 13. Electrophoretic pattern (Tiselius) of the serum of a patient with multiple myeloma. The paraprotein peak seems to straddle alpha$_2$ and beta globulins. Further determinations of the mobility showed this peak to be in the range of beta globulin. The disease in this patient had a fulminating course.

course has been described in the rare cases of this type of myeloma.[93-95]

5. Multiple myeloma with minor changes in serum protein. From 10 to 15 per cent of patients with multiple myeloma have a normal or nearly normal electrophoretic pattern of the serum proteins or only a moderate decrease of gamma globulin (figure 14). They may even have the electrophoretic pattern of agammaglobulinemia. In our experience as as well as in that of others,[87] these patients have the least malignant clinical course. The life expectancy after diagnosis is often several years. Initially, the anemia is only of moderate degree, although bone lesions and bone pain may be present as in other types of myeloma. The terminal course often is precipitated by the development of "myeloma kidney," or obstruction of the nephrons with protein casts and progressive uremia.[78, 87]

In this type of the disease, the abnormal product of the myeloma cells usually is not found in the serum, because the molecular weight and size are about half those of albumin. Therefore, it passes the glomerular filter and appears in the urine as Bence Jones protein. While the incidence of Bence Jones protein in all cases of multiple myeloma is only 50 per cent, this protein is found in nearly every case of the group with minor serum pro-

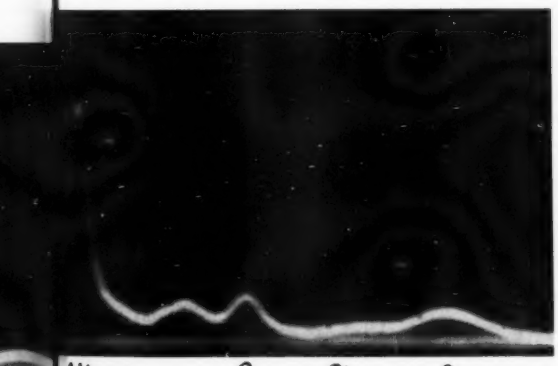

FIGURE 14. Electrophoretic pattern (Tiselius) of the serum of a patient with multiple myeloma. The serum contains no paraprotein peak. The only abnormality is a decrease of gamma globulin. The patient lived four and a half years after the diagnosis of multiple myeloma was established. His urine contained large amounts of Bence Jones proteins (see figure 15).

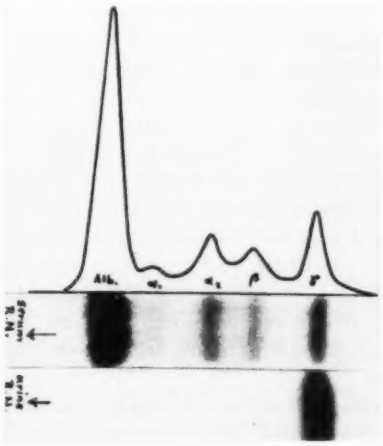

FIGURE 15. Electrophoretic pattern (filter paper) of serum (upper strip) of patient with multiple myeloma represented in figure 14, shortly before his death. A new abnormal peak had appeared in the serum within the migratory range of gamma globulin. It was identical with the Bence Jones protein peak in the urine (lower strip) and actually represented Bence Jones proteins that had been retained in the serum. The patient was in severe renal failure at that time. Necropsy established the presence of "myeloma kidney" with protein casts as the anatomic basis for uremia.

tein changes.[96,97] Electrophoresis of the serum may establish the diagnosis of multiple myeloma in only 90 per cent of cases, but simultaneous electrophoretic examination of the serum and urine will make it possible to diagnose nearly all cases.

The molecule of a Bence Jones protein not only is smaller than that of albumin, but it also is deficient in methionine, an essential amino acid present in all other normal and abnormal human proteins. The Bence Jones proteins are not identical in all patients; in each case they have individual characteristics that distinguish them immunochemically from the Bence Jones proteins of other patients.[85,98,99] They are incomplete, abortively formed proteins and perhaps unfinished precursors of normal globulins.[100-103] In the electrophoretic pattern, they appear as slender peaks traveling anywhere between gamma and alpha$_2$ globulins.[104]

Patients who excrete large amounts of Bence Jones proteins in the urine are subject to the development of protein casts in the renal collecting tubules.[78,105,106] One is tempted to speculate that these protein casts actually might consist of Bence Jones proteins which were precipitated in the more acid urine in the distal part of the nephron. It is hard to substantiate this point, since the protein of these casts is denatured and difficult to identify. As increasing numbers of nephrons are obstructed and destroyed, uremia finally ensues with associated acidosis and anemia. At this stage, not all the Bence Jones proteins may be excreted into the urine. A portion may be retained in the serum, where it forms an abnormal peak in the electrophoretic pattern (figure 15).[84,98,107]

There is no definitive therapy for multiple myeloma at this time. Various agents have been used palliatively. They are difficult to evaluate, since the life span of patients varies greatly in the natural history of the disease. Urethan sometimes seems to exert a transient inhibitory influence on the progress of the disease.[87,96,108,109] ACTH and the adrenal corticosteroids effect a decrease in the number of plasma cells in normal persons and induce a decrease of the antibody concentration of the serum in hyperimmunized rabbits.[110] In man, treatment with steroids has resulted in temporary remission of subjective symptoms as well as a drop of serum globulins in some cases.[111-113] Nitrogen mustard in combination with urethan also has seemed to exert some palliation.[114] One report of complete clinical and hematologic remission of multiple myeloma following severe hepatocellular damage with hepatic coma poses some intriguing questions.[115]

Recognition of the dysproteinemias has presented many problems, few of which have been answered satisfactorily. Their elucidation will help not only in management of this group of diseases but also in understanding the mechanism of protein synthesis and the relation to other physiologic systems and various pathologic states.

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Design and Clinical Application of the Helix Reservoir Pump-Oxygenator System for Extracorporeal Circulation

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AFTER a number of years of slow development, total cardiopulmonary bypass utilizing an extracorporeal circulation has in the past several years matured into a technic widely used to bring relief to a steadily increasing variety and number of patients afflicted with heart disease.

The successful clinical application of visual intracardiac surgery depends on the design of the pump-oxygenator and its method of application, the use of correct surgical technics, and the proper postoperative management of the patient.

Clearly, the safety and efficiency of a pump for temporarily replacing cardiac action and of an artificial oxygenator for supplanting similarly the functions of the lungs in man bear a very important relationship to the design and construction of the apparatus.

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The present report proposes to supply certain details of design and application of a metabolically efficient,[1,2] uncomplicated pump-oxygenator system which has been developed during many hundreds of hours of use in the experimental laboratory,[3] supplemented by ob-

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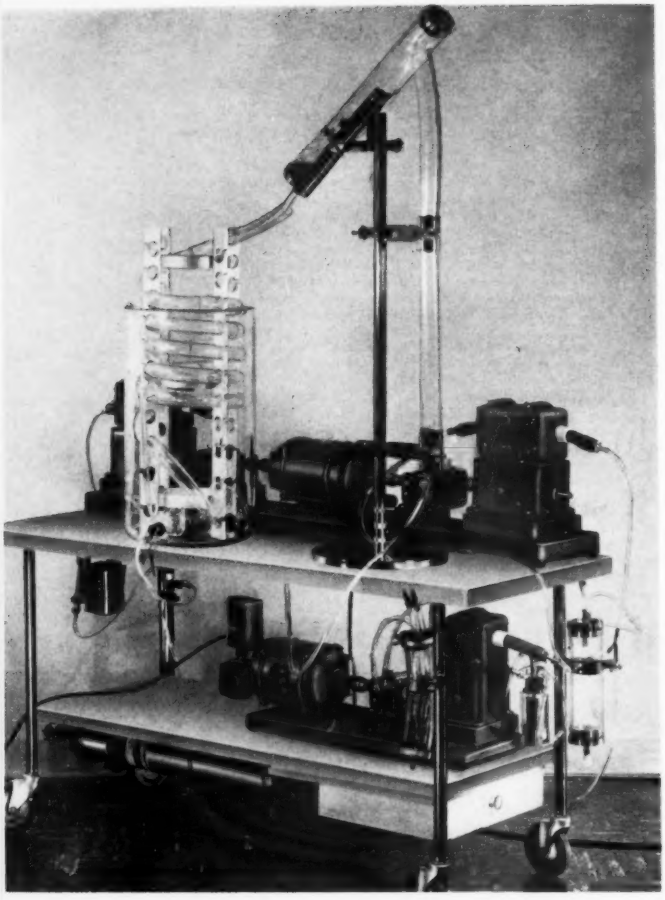

FIGURE 1. Pump-oxygenator utilized for visual intracardiac surgery. The pump consists of a single explosion-proof electric motor which activates two pump heads (arterial and venous), each equipped with an individual speed changer, all mounted on a single base. The artificial (large bubble) oxygenator has no moving parts, is sterilized by autoclaving, and is constructed entirely of polyvinyl plastic tubing, which is discarded after each perfusion. From right to left may be noted the vertical mixing tube, the inclined debubbling chamber and the helix reservoir immersed in a constant-temperature water bath. The venous blood is drained from the patient's caval cannulas by gravity flow into the plastic reservoir (attached to the leg of pump table farthest to the right). From this reservoir it is circulated by the venous pump to the mixing tube. From the lower end of the helix, the oxygenated blood is returned through disposable filters to the patient's arterial system. The oxygen enters the venous blood directly through a nylon plastic diffusion plate at the base of the mixing tube. The venous blood carbon dioxide escapes with the excess oxygen during oxygenation. The coronary sinus return pump and plastic reservoir (attached to the table leg in the lower foreground), for returning to the oxygenator blood aspirated from the open heart, are seen on the lower level. For flow rates over 2000 to 2500 cc. per minute a double mixing tube and debubbler are used with the single helix reservoir.

servations in 350 clinical perfusions,[4-6] some lasting as long as two hours. The entire system has been found eminently satisfactory for daily use.

The reparative intracardiac surgery made possible by this apparatus has substantially altered the outlook for patients afflicted with congenital and acquired heart disease.[7]

The Helix Reservoir Bubble Oxygenator

The helix reservoir bubble oxygenator* consists of three major components: the blood-oxygen mixing tube, the debubbling chamber and the helical reservoir. In addition, other units are the filter, the venae cavae drainage reservoir, and the cardiotomy return system (figures 1 and 2). The size of the oxygenator is adapted to the size of the patient and the approximate desired perfusion rate (table 1). The blood-oxygen mixing tube is a vertical column of flexible polyvinyl tubing in which the venous blood is filmed on the surface of large bubbles of 100 per cent oxygen. This admixture of venous blood and oxygen gently rises in the mixing tube due to the venous blood entering and the flow of oxygen passing up the tube. At the base of the mixing tube is placed a nylon plastic cylinder closed at the top by a nylon plate (figure 3). This plate has a central perforation large enough to accommodate the conduit carrying venous blood from the patient to the oxygenator. This hole is surrounded by 12 dozen perforations approximately the size of a No. 23 hypodermic

*The component parts are produced by the Phelan Manufacturing Company, 2029 Washington Avenue South, Minneapolis, Minnesota.

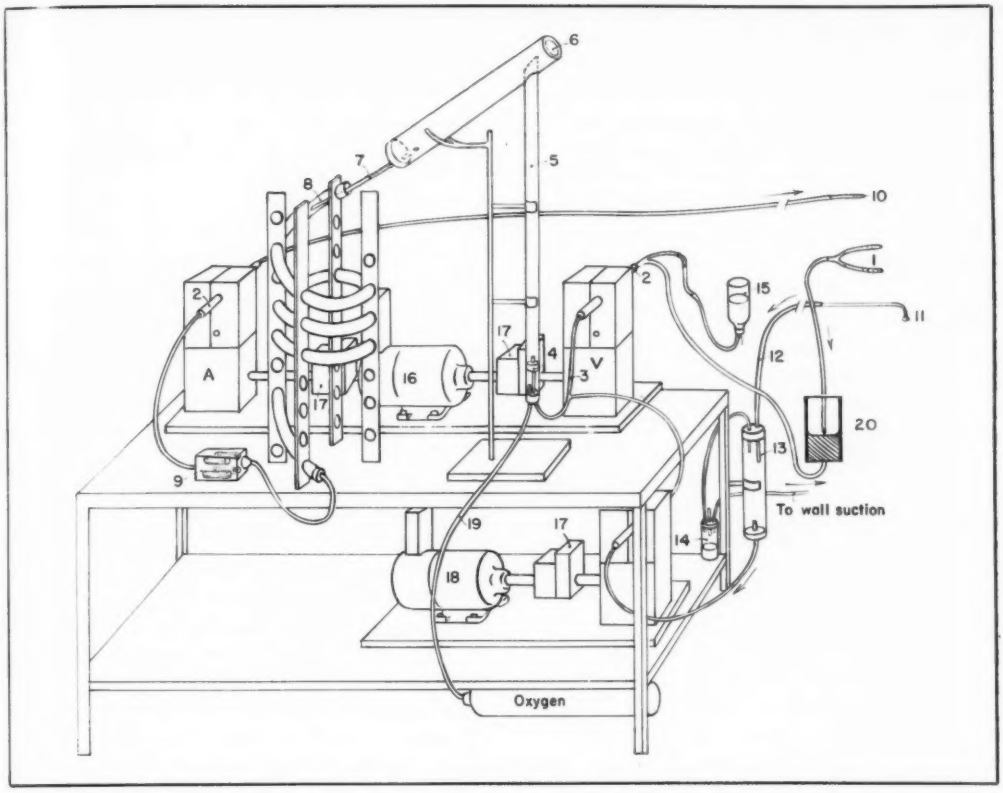

FIGURE 2. Diagrammatic illustration of the extracorporeal pump-oxygenator circuit.

1. Venae cavae catheters*
2. Latex rubber pump hoses
3. Heat-sterilized polyvinyl tubing†
4. Nylon plastic oxygen dispersion plate
5. Mixing chamber†
6. Debubbling chamber†
7. Connecting tubing† for gravity flow of arterialized blood
8. Helix reservoir† (immersed in constant-temperature water bath at 41° C.)
9. Arterial filters
10. Arterial catheter*
11. Cardiotomy aspirator
12. Polyvinyl tubing
13. Cardiotomy return reservoir†
14. Mercury trap to regulate negative pressure in system
15. Bank blood for priming and transfusion of system
16. Explosion-proof electric pump motor
17. Speed regulators for pumping heads
18. Cardiotomy return pump
19. Oxygen inlet to oxygenator
20. Gravity venous reservoir†

*Plastic catheters, which can be autoclaved, are specially designed for caval and arterial cannulations and can be obtained from C. R. Bard, Inc., Summit, New Jersey.

†Polyvinyl plastic, a product of Mayon Plastics, 415 17th Avenue North, Hopkins, Minnesota.

needle bore. Oxygen is directed into the base of the mixing tube through these perforations.

A properly designed oxygen dispersion plate presents minimal resistance to the inflow of oxygen. If such is not the case and oxygen is introduced under unusual force, the energy generated, as measured by the pressure in the line transmitting oxygen to the system, will be imparted to the blood via the gas jets created, causing unnecessary hemolysis. The oxygen dispersion plate, as described, presents only a few millimeters of mercury pressure resistance to a flow of gas up to 12 l. per minute. This maximal quantity is more than has been need-

TABLE 1

DIMENSIONS OF PLASTIC TUBING COMPONENTS FOR THE HELIX RESERVOIR BUBBLE OXYGENATOR (INSIDE DIAMETER AND LENGTH)

PERFUSION RATE (cc./min.)	MIXING TUBE		DEBUBBLER		HELIX	
	I.D. (in.)	length (cm.)	I.D. (in.)	length (cm.)	I.D. (in.)	length (cm.)
To 1000	1½	65	2½*	55	1	350
1000 to 2000	1½	80	2½	55	1	450
2000 to 2500	1½	95	2½	55	1¼	550
2500 to 5000†	1½‡	65 to 75‡	2½§	55§	1¼	550 to 650

*The 2½ in. inside diameter plastic tubing is also used for the venae cavae gravity drainage reservoir and the cardiotomy return reservoir. The latter two chambers are made 25 to 30 cm. in length (figures 4 and 5).

†A double system is used for these flow rates (figure 5).

‡Two mixing tubes of these dimensions.

§Two debubblers of these dimensions.

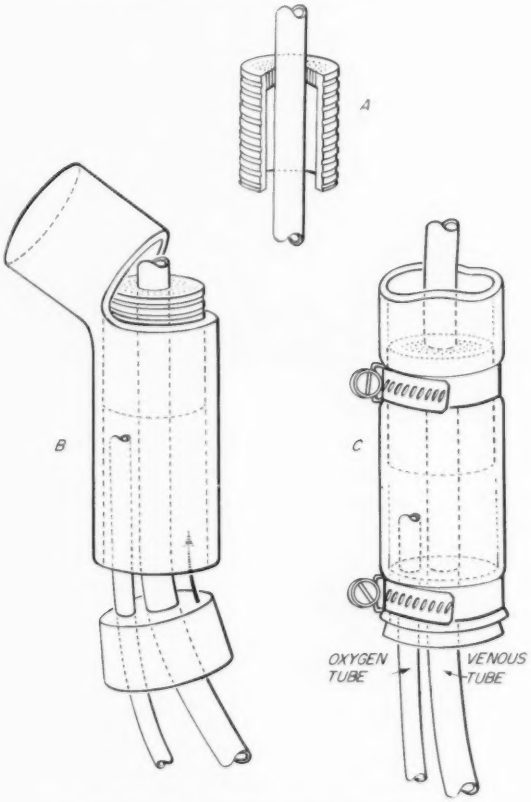

FIGURE 3. Design of oxygen dispersion plate.
A. Nylon dispersion plate, which can be autoclaved, with central orifice for the unoxygenated venous return and the multiple (144) perforations (equal bore No. 23 needle) for oxygen entry.
B and C. Details of placement of the dispersion plate into base of mixing tube and its fixation.

ed in clinical usage. The pressure in the gas line during the perfusion also will be elevated by an amount equal to the hydrostatic pressure of the blood which the column of gas supports in the mixing tube.

The blood-oxygen mixing tube empties from its top into a polyvinyl debubbling chamber. This chamber is designed to separate the excess oxygen and carbon dioxide from the arterialized blood. A double-barreled mixing tube and debubbler is used for perfusions likely to require flows of over 2500 cc. per minute (figure 5). This provides the larger debubbling surface necessary for these higher perfusion rates. A spare sterilized debubbling chamber is always available and this may be inserted without interruption of the perfusion should it become ineffective during an unusually prolonged bypass.

The blood flows by gravity through the debubbling chamber and empties into the helical reservoir where effective removal of any free gas remaining in the blood is achieved. The helical reservoir carries out this function by taking advantage of synergistic physical forces. Free gas remaining in the blood gives it a lesser density than that of normal blood, and consequently this less dense blood is forced upward by hydrostatic pressure. This lighter blood containing free gas therefore laminates on the upper layer within this tube. As the flow of blood is down the inclined plane of the helix, the heavier gas-free blood descends by

gravity beneath the lighter gas-containing blood, forcing it continuously upward. This lamination of the flow is present as long as blood of the two densities is present; however, following a short transit down the tube the gas coalesces and rises upward, and oxygenated blood, free of the excess gas, flows to the bottom of the helical coil where it leaves through the arterial filters.

All of the plastic components of the helix reservoir oxygenator which are in contact with the blood are made of a pure polyvinyl tubing* sterilized in the steam autoclave before use. They are discarded after one application, as their cost is less than the expense or potential dangers to the patient of attempting to clean and reuse them.

The caval drainage system—A gravity drainage system[8] of the venae cavae is preferred to direct pumping, as the former aids in preventing abnormal pressure rises in the patient's venous system and thus contributes to smoother perfusions. Figures 1, 4 and 5 illustrate the system used. The reservoir chamber is of disposable heat-sterilized polyvinyl tubing with polished stainless steel end plates. The lower portion of this well need not be more than 20 in. below the level of the patient's cavae. After starting the perfusion this chamber may be adjusted to a suitable level dependent on the particular patient's venous pressure and blood volume and the flow rate being used. This running level often is found to be about 12 in. below the level of the cavae. If the reservoir is placed too low, the siphoning forces of the column of blood may become excessive and tend to occlude the cavae against the catheters.

The cardiotomy return system—In clinical operations the blood from the cardiotomy must, of course, be returned to the extracorporeal system. The assembly of this system is portrayed in figure 6. Figures 4 and 5 show the dimensions used. A ⅜ in. internal diameter polyvinyl hose is used to conduct the blood from the aspiration tip to the collection vessel. A hose of this size will return a greater quantity of blood with less vacuum than a smaller hose, and it is not too large for convenient manipulation. The aspiration vacuum is set at 15 to 20 mm. of mercury but can be altered as the indications arise. The lowest aspiration pressure that is effective is desirable, but hemolysis does not come as much from a high vacuum per se as from the turbulent mixing of air with the blood.

If the need arises to remove rapidly a large quantity of blood, as from the open heart of a patient with mitral disease and some aortic valve incompetence, or in the case of many patients with cyanotic heart disease and a well-developed bronchial collateral circulation, the high vacuum source can be used without a proportionate increase in trauma to the blood, as minimal amounts of air are mixed with the aspirated blood in such situations. When the need to remove such large quantities of blood passes, the vacuum in the cardiotomy collection reservoir can be returned to the desired level by releasing the clamp on the air vent hose. The cardiotomy aspiration chamber is placed as close to the floor as practical, as this increases the siphoning effect on the aspiration tip without need for increasing the vacuum source. To reduce the resistance in the aspiration tube itself, it should be as short as practical usage permits. The aspirator should also be held as horizontal as possible, as each centimeter of vertical elevation increases the vacuum that is necessary to move the column of blood.

A second or spare inlet (figures 4 and 5) is made available into the cardiotomy return vessel which can be connected to a second aspiration tip or catheter. This is used to catheterize an anomalous left superior vena cava, or whenever a large blood loss is anticipated, as with the types of cardiac lesions previously described, two cardiotomy aspirators are routinely attached to this reservoir.

This system will handle up to 3000 cc. per minute, and, while this capacity may sound excessive, we have occasionally encountered flows out of the open heart approaching this quantity. An efficient cardiotomy return system has often made the difference between success and failure in clinical practice.

Oxygen supply to the oxygenator—Various mixtures of oxygen with carbon dioxide have

*Mayon Plastics.

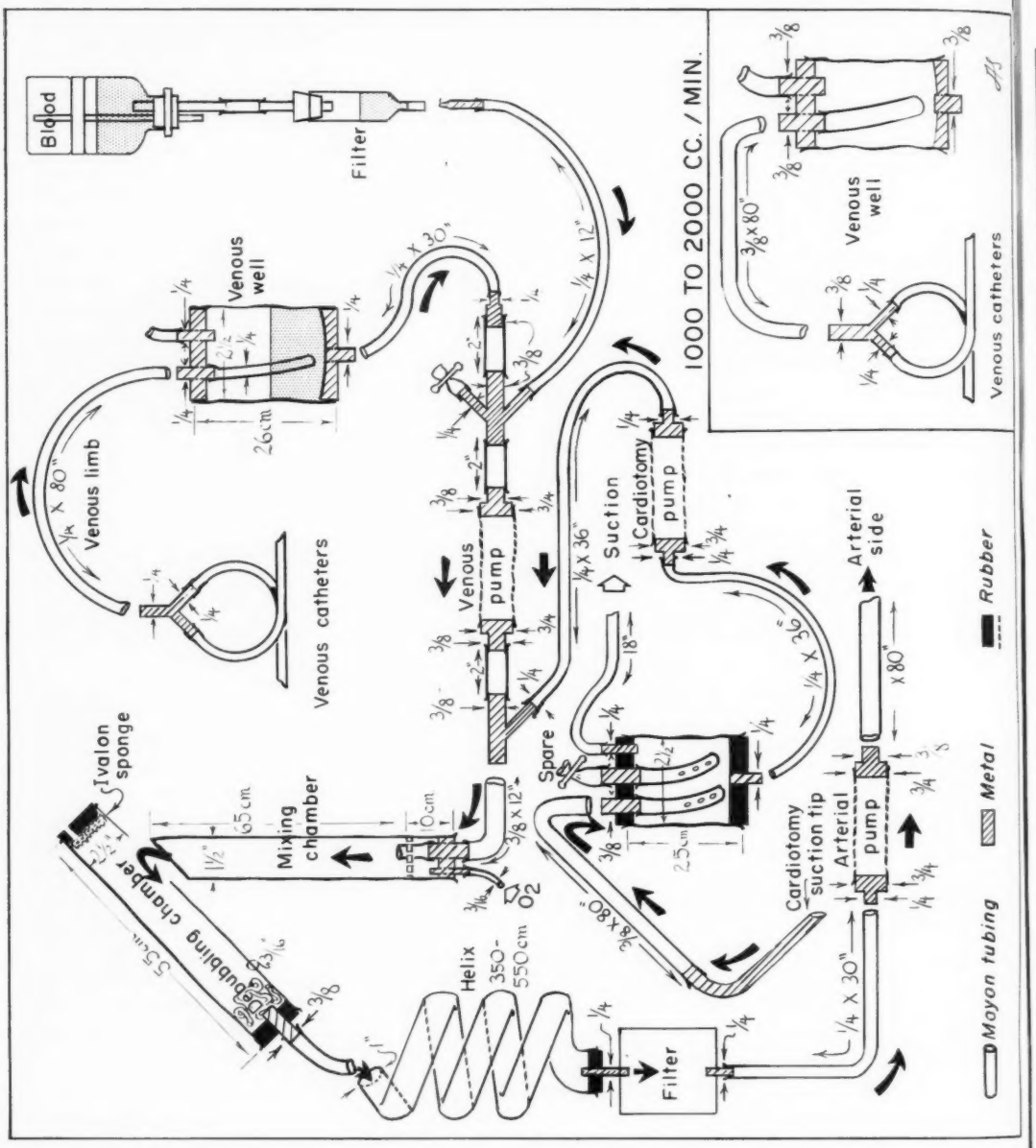

FIGURE 4. Assembly of helix reservoir bubble oxygenator for flows from 500 to 1000 cc. per minute. All dimensions are in inches except where otherwise indicated. All measurements of diameter of tubing, chambers and adapters refer to inside diameter (inches). All metal connectors and adapters are specially designed, internally polished stainless steel. For flow rates of 1000 to 2000 cc. per minute the diameter of the venous return tubing is increased (inset).

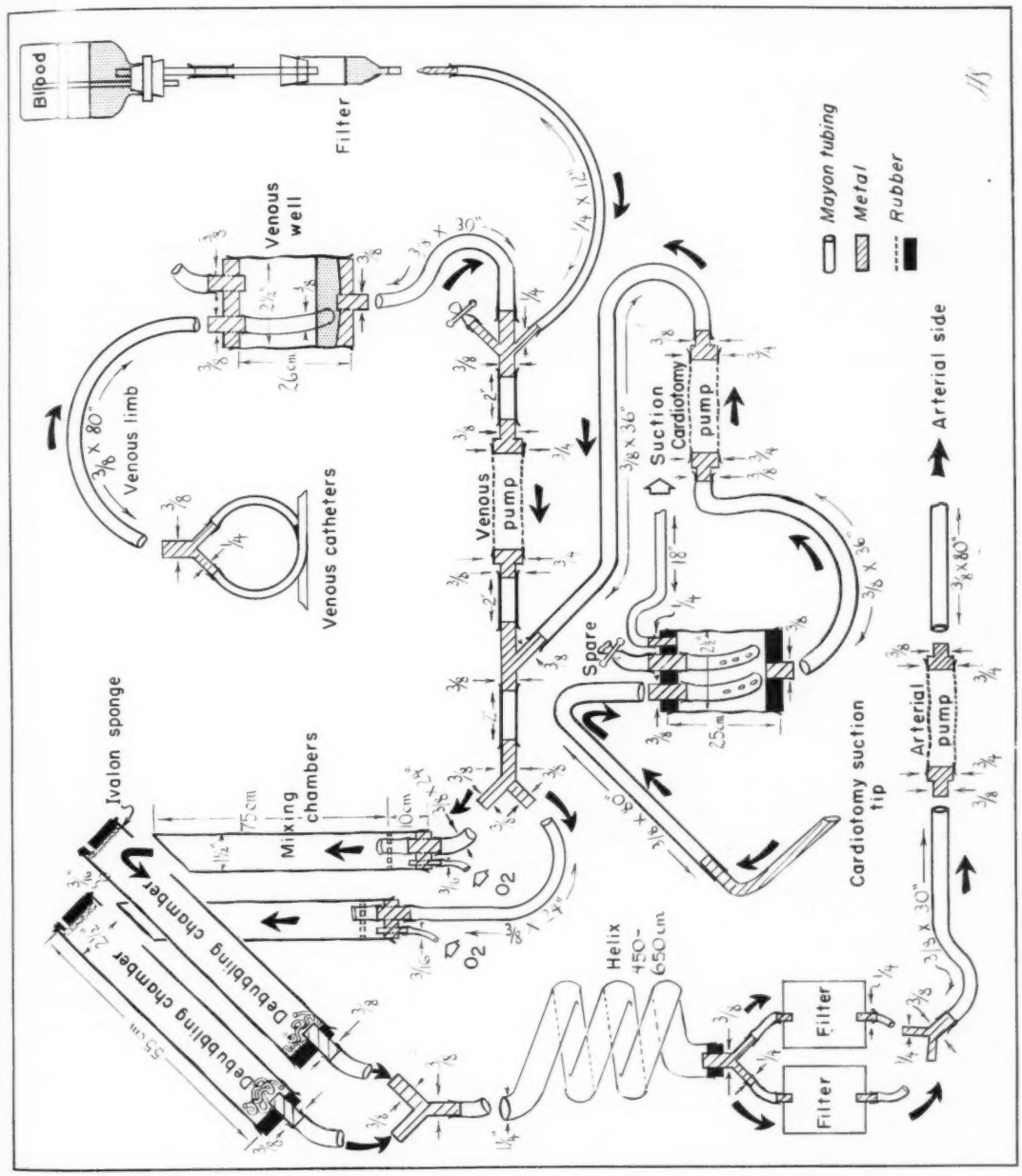

FIGURE 5. Assembly of helix reservoir bubble oxygenator for flows from 2000 to 5000 cc. per minute.

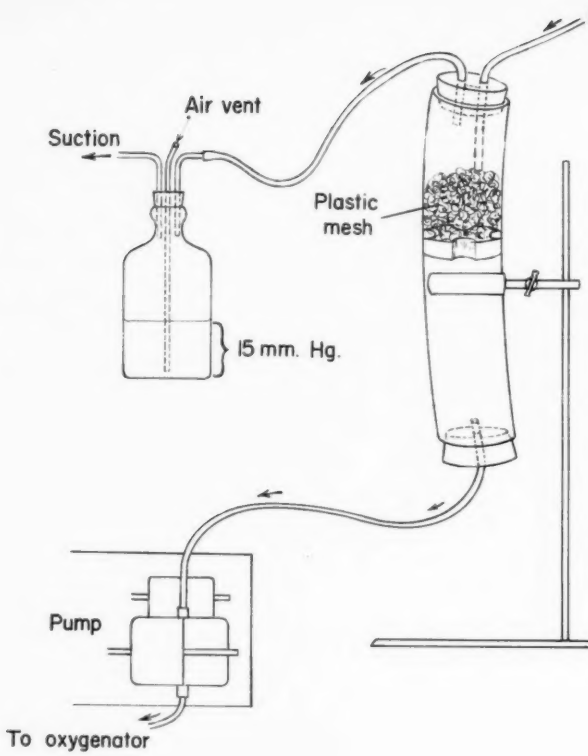

FIGURE 6. System for returning cardiotomy blood losses. The main body of the chamber is of the same polyvinyl hose (I.D. 2½ in.) as is used for the debubbler chamber; it is 12 to 16 in. in length. Polished stainless steel end plates are now used for this reservoir chamber in place of the rubber stoppers shown. As indicated in figures 4 and 5, a spare cardiotomy inlet is always available for use of a second sucking system where blood losses are large. Should the occasion arise to remove a large quantity of blood rapidly, the air vent on the mercury trap can be closed until the need for increased suction has passed. This system will aspirate and return up to 3000 cc. per minute.

been tested in the helix reservoir oxygenator; however, none has had demonstrable advantages over the use of 100 per cent oxygen. We have found no evidence of oxygen toxicity under the conditions in which it is used in this apparatus. One of the important safety features of this system in that regard is the efficiency with which the temperature of the blood in the oxygenator is maintained.

The oxygen input to the mixing tube is three to five times the blood input. During all perfusions repeated determinations of oxygen content and oxygen capacities have been made on the oxygenated blood. These values are routinely checked after the perfusion and serve as a guide to the oxygenator technician. The arterial blood leaving the oxygenator is maintained at 95 to 98 per cent saturation.

Connectors and filters—Some of the hemodynamics that are concerned with connectors and filters have previously been described.[3] Suffice it to say that dead space at connections must be avoided, as such a defect may form a potential area for fibrin and platelet clot formation due to eddy currents at these sites. We have designed stainless steel connectors and adapters,* smoothly polished internally and without abrupt shoulders or other obstructions, which obviate much of the potential turbulence at these sites (figure 7).

At the present time we are using standard infusion set filters.† These filter cartridges are fitted into a specially designed methacrylate chamber* which holds four filter units. For perfusions of less than 2000 cc. per minute one chamber containing four filters is used. For perfusions of over 2000 cc. per minute two chambers containing eight filter cartridges

*Phelan Manufacturing Company.

†Baxter Laboratories, Morton Grove, Illinois, Filter #CLFIB.

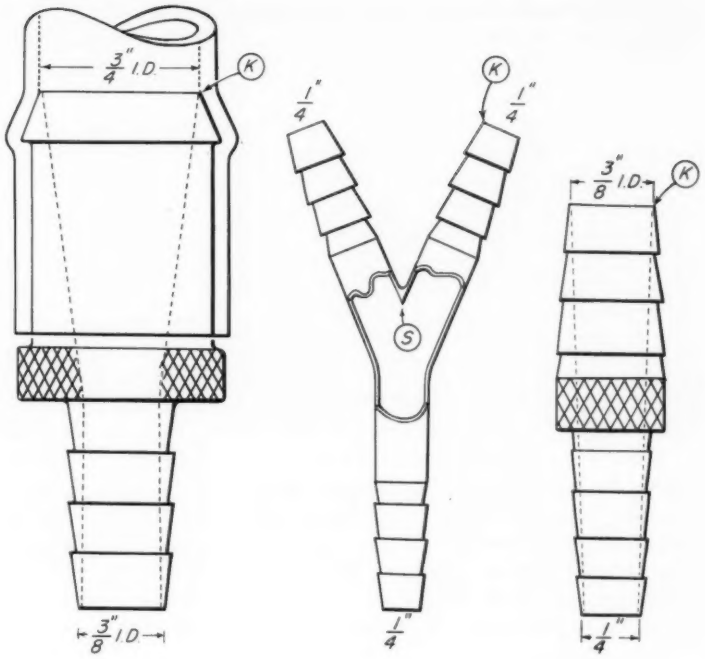

FIGURE 7. Stainless steel adapters and Y connectors are specially designed to eliminate all rough shoulders and dead spaces at the tubing-metal junction where fibrin formation may occur; they are internally polished. Attention to these details is most important in eliminating blood trauma and emboli through provision of streamlined flow.

are used. Each filter cartridge has a filtration area of 50 sq. cm.

We prefer a rigid arterial filter. A supple socklike filter system will tend to vibrate or flap with the pulsatile forces of the pump. This oscillation may damage the blood and cause deposition of fibrin which may embolize beyond the filter mechanism. Obviously, a poorly designed arterial filter can cause more difficulty than no filter at all.

Connecting hoses—Polyvinyl tubing of ¼ in. inside diameter is used to connect the patient to the oxygenator for perfusions of up to 1000 cc. per minute. Above this figure the resistance in this size tubing becomes significant and, in turn, is reflected as a reduced efficiency of the pumps. Therefore, ⅜ in. inside diameter plastic tubing is used for all perfusions of over 1000 cc. per minute.

Preparation and sterilization of plastic tubing—The new polyvinyl tubing is cut to the desired lengths and washed with a laboratory detergent.* After thorough rinsing in water and coating of the indicated areas with the antifoam silicone,† the open ends of the tubes are wrapped with gauze which is held in place by special self-sticking autoclave tape. Each hose is then wrapped in a double-thickness canvas. The wrapped hoses are then placed into an autoclave; care should be taken that one hose does not overlie another, as this will cause them to become indented when heated. The autoclave is set for 250° F. and 20 lb. pressure for one-half hour. The autoclave is set to "steam exhaust" and the hoses are dried under a mild vacuum at 150° F. for one to three hours, depending on the thickness of the sterilizing canvases. This drying is an important step and if omitted the plastic tubing will be opaque rather than clear and transparent. Many units can be made up at a single time and stored in the operating suite until needed. Just prior to the operation the various hose units are assembled; it is obviously important not to contaminate any of the parts which will be exposed to the blood.

*ALCONOX®, Alconox Inc., Jersey City 4, New Jersey.

†Dow-Corning Corporation, Midland, Michigan.

Siliconing the debubbler and cardiotomy return vessel—ANTIFOAM A®* is used to coat the inside of the debubbling tube and the first 20 cm. of the helix. The caval reservoir and cardiotomy† return chambers do not ordinarily require Antifoam treatment. A gauze sponge soaked with the emulsion is used to place the thinnest possible layer of Antifoam in the above-mentioned units prior to autoclaving. If any excess has pooled in these vessels after autoclaving, it is removed by allowing it to drain out of the tubing before assembly. A very thin coating of Antifoam will perform its function better than a thick coat, as this substance is active in one part in 10,000,000. If a great excess of Antifoam is applied to the system, it can be swept into the arterial tree as emboli. The debubbling surface in the debubbling tube is increased by the placement of a small coil of plastic tubing which is also thinly coated by wiping the external surface with Antifoam-soaked gauze before autoclaving.

Priming the helix reservoir bubble oxygenator—The oxygenator reservoir is primed to contain a quantity of blood sufficient to provide at least a one minute circuit time through the oxygenator. This portion of the apparatus is therefore tailored to the size of the patient and the expected perfusion rate (table 1). The one minute circulation time provides an adequate buffer for control of the patient's blood volume and the perfusion in case of any unforeseen temporary imbalance between outflow and inflow. For example, should there suddenly develop a diminution in venous return because of some unexpected blood loss, the team has up to one minute to adjust for the difficulty without the necessity of decreasing the arterial perfusion to the patient.

A constant-temperature water bath is kept available in the operating suite and the bottles of heparinized blood are placed into this bath several hours before the operation to be sure that the blood has attained body temperature before it is used. The temperature of this bath is set at 41° C. This blood which is selected to prime the oxygenator directly is intercrossmatched. The priming bottles are attached to the venous reservoir of the oxygenator, the blood is put through the blood-oxygen mixing column for arterialization, and it subsequently fills the helix. The oxygen flow into the mixing column is adjusted so that it is barely adequate to push the blood through the column. This prevents the oxygen tension from reaching unusually high levels during priming. The priming blood should be as warm as or slightly warmer than the water bath (39° C.) that surrounds the helix reservoir. If the priming blood is colder than the helix bath and in addition has been inadvertently supersaturated, the dissolved oxygen will come out of solution as the priming blood is warmed within the helix reservoir water bath. Many minute bubbles of oxygen will then be deposited on the walls of the helix coil. These are probably harmless but, if such a circumstance does occur, it is better to wait a few minutes until the temperature of the blood in the helix coil has equilibrated with that of the bath and until all the excess oxygen in solution has been removed from solution to the walls of the tube. The perfusion can then be started. These minute bubbles will not move out of the helix as bubbles but will be absorbed by the blood which will subsequently pass through the helix reservoir.

Pumps for open heart surgery—The Sigmamotor pump‡ (figures 1 and 8) used in nearly all of the clinical cases has many desirable features: dependable mechanical performance; disposable surfaces in contact with the blood; ability to calibrate its output accurately, and the occlusive action of its pump fingers which insures the maintenance of calibrated flow rates in spite of the higher resistances often encountered in poorly developed patients with small arterial vessels for cannulation. This last feature makes it possible to maintain a normal systemic arterial blood pressure during the bypass interval even in patients with abnormally small arteries for cannulation.

*Dow-Corning Corporation.

†In cases in which an unusually large blood loss from the open heart may be anticipated we coat the cardiotomy reservoir with a thin film of Antifoam A.

‡Sigmamotor, Inc., 3 North Main Street, Middleport, New York. Pumps used are Models T-M1 or T-M2 and the coronary sinus return unit.

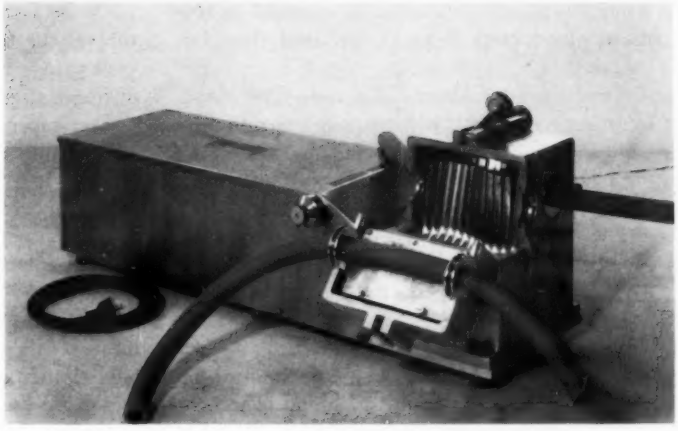

FIGURE 3. Cross-circulation pump for use in open heart surgery. This pumping unit (Sigmamotor T-M2) is occlusive in type and is similar to its predecessor (T-M1, shown in figure 1) in having two separate pump heads, each driven by an individually controlled speed changer and powered by a single electric motor. The major modifications relate to more compact size, lighter weight, lowered noise level and increased capacity as well as an improved method for inserting the pump tubing.

We have investigated both experimentally and clinically two types of nonocclusive blood pumps. These have been unsatisfactory for routine use in heart surgery because of the rapid fall-off in pump output which occurred with increased resistances,[9] resulting in subnormal blood pressures in the patient.

The suggestion made by some that occlusive pumps cause more hemolysis has not been borne out in fact. In 350 patients that we have operated on utilizing the Sigmamotor occlusive-type pump and the helix reservoir oxygenator and with varying perfusion durations of up to two hours, the mean plasma hemoglobin level was 52 mg. per cent (range 10 to 156 mg. per cent).

Pump calibration and perfusion rates—As the weight of each patient is known, an approximate perfusion rate is selected for him depending on his size and diagnosis. The arterial pump is then set by means of a stopwatch used to measure the rate of pumping sterile dextrose into a graduate. The venous pump is set at approximately the same level but the rate is altered during the perfusion, dependent on the venous drainage and the cardiotomy return. The perfusion rates are varied from 50 to 100 cc. per kilogram of body weight, with infants requiring the higher relative rate. As cyanotic patients have an appreciable bronchial collateral circulation and consequent shunting of blood from the aorta to the heart, they will often receive as much as 20 per cent more blood during the perfusion than patients who are acyanotic. After the onset of perfusion, the actual flow rate utilized for a particular patient depends on the systemic blood pressure and the monitoring electroencephalogram as indicated in the following paragraph.

Evaluation of the perfusion—Electroencephalograms* (four leads) are monitored throughout the perfusion, as are intraluminal arterial pressures, by means of a polyethylene catheter in the internal mammary artery. Once the perfusion has been started, the flow rate is adjusted to produce a normal systemic blood pressure. We have not used vasoconstrictors to raise blood pressure, preferring to accomplish this by adjusting the flow. With normal blood pressure the electroencephalogram virtually always remains unchanged from the preperfusion control.

Blood Preparation

Time for blood collection prior to the perfusion—Probably the best time to collect the blood to be used for priming and replacement during a perfusion would be immediately before its actual use. In practice we usually have collected the blood the day before the intended perfusion. This allows ample time for proper collection and unhurried crossmatching.

*We are indebted to our anesthesiology staff for introduction and continued use of this device.

After the blood is collected it is stored in the usual blood bank refrigerator until time for its use.*

Conditions for blood collection—The blood is drawn by gravity without vacuum into siliconized bottles.† It is our belief that the frothing produced by the usual vacuum bottle may be damaging.

The priming blood destined to be mixed directly in the reservoir is intercrossmatched, while the remainder of the blood is crossmatched with that of the patient.

Anticoagulants—Twenty milligrams of heparin in 30 cc. of normal saline solution is added to each 500 cc. unit of blood. The collection bottle should be rotated continually while the blood is being drawn to insure adequate mixing. This amount of heparin is sufficient to prevent coagulation for at least 24 hours. The units of blood not used at the surgical procedure are returned to the blood bank where sodium citrate is added and the blood is given over for general use.

Ordinary bank blood (collected in A.C.D. solution) is used to replace the patient's blood losses until time for heparinization of the patient and insertion of the cannulas. Immediately after the perfusion is concluded and protamine or polybrene has been given, the citrated blood is again used for all replacement needs.

Preparation of the Patient

Weighing the patient—The patient is accurately weighed in the operating suite before being anesthetized and again immediately after the operation. This has proved to be the most accurate and rapid method to ascertain the patient's blood volume immediately after the perfusion.

Temperature control—A water circulation blanket is used on the operating table to maintain the patient euthermic throughout the operation. A constant-reading rectal thermometer is used to monitor the patient's temperature while he is on the blanket, and the temperature of the thermal blanket is altered as necessary to maintain the patient's temperature at the desired normal level.

For successful clinical perfusions of any appreciable duration, external heat must be applied to the blood circulating through the extracorporeal apparatus both to prevent a fall in the patient's body temperature with the consequent cardiac depressing effects of hypothermia and to prevent air embolism. If the blood in the pump-oxygenator (whether it be bubble, film or membrane type) is allowed to cool significantly, it will release oxygen bubbles from the plasma on entering the arterial system of the warmed patient. In the system herein described the helix reservoir is immersed in a water jacket thermostatically controlled at 41° C.

By these methods adequate temperature control has been regularly achieved even for perfusions of long duration.

Thoracotomy incisions for open cardiotomy—For almost all congenital cardiac lesions the midline sternotomy has numerous advantages over the bilateral anterior thoracotomy with a transverse sternotomy. These advantages may be summarized as follows: The pleural cavities are not entered, and the prevention of retraction and drying of the lungs greatly reduces the incidence of postoperative secretions and pneumonitis; less heat loss occurs during operation; shorter operating time is required; fewer sources for postoperative bleeding are created, and smoother convalescence results due to lack of injury to chest wall muscles; the more rigid repair of the sternum possibly results in lessened pain and better coughing.

For almost all the acquired lesions of the aortic or mitral valves the right posterolateral incision through the bed of the fourth or fifth rib is preferred.

Cannulations—A common femoral artery catheter will provide the easiest access to the patient's arterial system and eliminate some of the dissection within the chest. This vessel may occasionally be of insufficient size, especially in infants, and in such cases the left subclavian artery can be used for the arterial cannulation. Subclavian artery cannulations

*The Blood Bank at the University of Minnesota is under the direction of Newell Ziegler, M.D.

†Specially prepared bottles containing 20 mg. of heparin in 30 cc. of normal saline solution are made by Baxter Laboratories.

have the theoretical danger of producing turbulent jets of blood at the origins of the innominate or left carotid arteries and thus increasing the resistance to blood flow to the brain; however, we have never actually demonstrated this to happen. If a right subclavian artery cannulation becomes necessary, the catheter should not be inserted far enough into the vessel to occlude the right common carotid origin. The venae cavae catheters should be placed well up into the cavae and have multiple fenestrations. The cross-sectional area of the caval catheters should be about one-half the cross-sectional area of the cavae. Larger caval catheters will prevent adequate atrial filling when the perfusion is not in progress, and smaller catheters may result in inadequate drainage of the cavae during the perfusion.

Heparinization of the patient—From 2.5 to 3 mg. per cent heparin in the circulating blood has proved to be a safe anticoagulation level for perfusions lasting up to two hours. Time intervals beyond this have not been investigated clinically. If the circulating heparin during the perfusion is less than 2 mg. per cent, the blood may clot after about 20 minutes. The heparin level in the priming and replacement bottles is about 4 mg. per cent (20 mg. per 500 cc. bottle). The patient's blood volume can be estimated (10 per cent of his body weight) and a quantity of heparin given to provide a heparin level of 2.5 to 3 per cent after dilution by the priming blood. The heparin dose given to the patient depends on his size and the size of the reservoir. For infants and children 1.5 mg. of heparin per kilogram of body weight will suffice, while adults require from 2 to 2.5 mg. of heparin per kilogram of body weight.

Heparin neutralization—More meticulous hemostasis is absolutely essential during these open heart procedures, as the patient who has been heparinized obviously will bleed more than an unheparinized person. However, with this additional attention to hemostasis, postoperative hemorrhage rarely is a problem except under unusual circumstances (extensive adhesions requiring mobilization).

Immediately after conclusion of the perfusion, an empiric dose of protamine sulfate is administered to the patient. The quantity has been calculated as twice the heparin dose administered at the time of initial heparinization to allow for the fact that the patient's final heparin level is somewhat higher than the amount initially given to him due to the additions contained in the replacement blood and blood from the oxygenator reservoir.

Since polybrene became available to us it has completely replaced protamine, as we concur in the opinion that it is a superior drug for heparin neutralization.[10] Polybrene has been used in a 1:1 ratio against heparin.

As soon as the chest tubes are placed, and prior to closure of the thoracotomy, they are attached to an aspiration source. This is to measure and replace any blood which may collect while the chest is being further closed, as well as to prevent clotting and obstruction of the drainage catheters.

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PAUL C. HODGES

New monthly feature to start in June

Radiology

for Practicing Physicians

WITH the June issue, POSTGRADUATE MEDICINE will inaugurate "Radiology for the Practicing Physician," a special monthly department which will cover various phases of the field of radiology as it concerns the practicing physician. Dr. Paul C. Hodges, since 1928 professor and chairman of the Department of Radiology of the University of Chicago, will conduct this special section. Current and projected aspects of radiology that will be of interest and help to general physicians will be emphasized. Whenever appropriate, Dr. Hodges will include roentgenographic reproductions, either selected from his own extensive records or provided by associates and former students in various parts of the world.

Dr. Hodges will welcome suggestions from readers as to subjects they would like to have him discuss. Suggestions and comments may be sent to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

While Dr. Hodges and his contributions to the field of radiology are widely known, the Editors believe that a brief biographic review would be of interest.

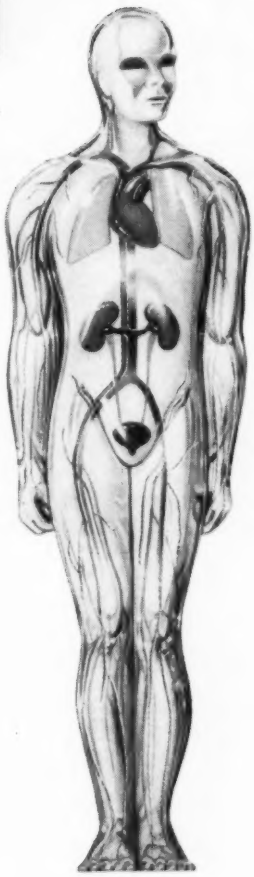
Two years before Roentgen discovered x-rays, Paul C. Hodges was born in Anderson, Indiana, in a hospital owned and operated by his surgeon father. His youth was spent in Ashland, Wisconsin, where his uncle, Dr. W. T. Rinehart, and his father were partners in a hospital the uncle had started earlier.

Dr. Hodges' interest in radiology began as a hobby practiced with his uncle in Ashland during high school and continued during undergraduate schooling at the University of Wisconsin in Madison, and in the Red Cross Hospital of the Harvard Medical School in Shanghai, China, in 1915 and 1916. Following this period, he finished his medical studies at Washington University in St. Louis, graduating in 1918. After service in the Army Medical Corps, Dr. Hodges was appointed to head the Department of Roentgenology at the newly established Peking Union Medical College of the Rockefeller Foundation in Peking, China. He served there from 1919 to 1923 and from 1924 to 1927. In 1923-24, on leave from this post, he continued work in physiology at the University of Wisconsin and received the Ph.D. degree there in June 1924.

Dr. Hodges, who will be professor emeritus July 1, 1958, has trained approximately 100 specialists in radiology. He has served as secretary and chairman of A.M.A. Section of Radiology, as president of the American Roentgen Ray Society, as a member of various national committees, and as consultant to several government agencies. He is a member of numerous professional organizations and holds honorary membership in radiologic societies in this country and abroad.

as simple
as 1-2-3
in

HYPERTENSION



1 INITIATE 'DIURIL' THERAPY
'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day.

2 ADJUST DOSAGE OF OTHER AGENTS
The dosage of other antihypertensive medication (reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response. If the patient is established on a ganglionic blocking agent (e.g., 'INVERSINE') this should be continued, but the total daily dose should be *immediately* reduced by 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.

3 ADJUST DOSAGE OF ALL MEDICATION
The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

BENEFITS:

- improves and simplifies the management of hypertension
- markedly enhances the effects of antihypertensive agents
- reduces dosage requirements for other antihypertensive agents—often below the level of distressing side effects
- smooths out blood pressure fluctuations

INDICATIONS: management of hypertension

Smooth, more trouble-free management of hypertension with 'DIURIL'

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.

• RAPAK

DESCRIPTION: A new approach to packaging surgeons' gloves which delivers them ready for the sterilizer, this pack holds one pair of the gloves, put up in a double envelope of two-way stretch crepe kraft, and a packet of BIO-SORB® (Ethicon). The gloves, dusted with the Bio-Sorb, have gauze pads in each wrist and a disposable soft paper drape. Each package is sealed with color-indicator tape on which glove size is stamped. The kraft paper wrapper is reusable. For those who prefer muslin, a companion economy pack is available in a single envelope, containing gloves without gauze pads in the wrists. This package can be sterilized in a muslin outer wrapper. Both packs are available in glove sizes 6 to 9.
PRODUCER: The Wilson Rubber Company, division of Becton, Dickinson and Company, Canton, Ohio.

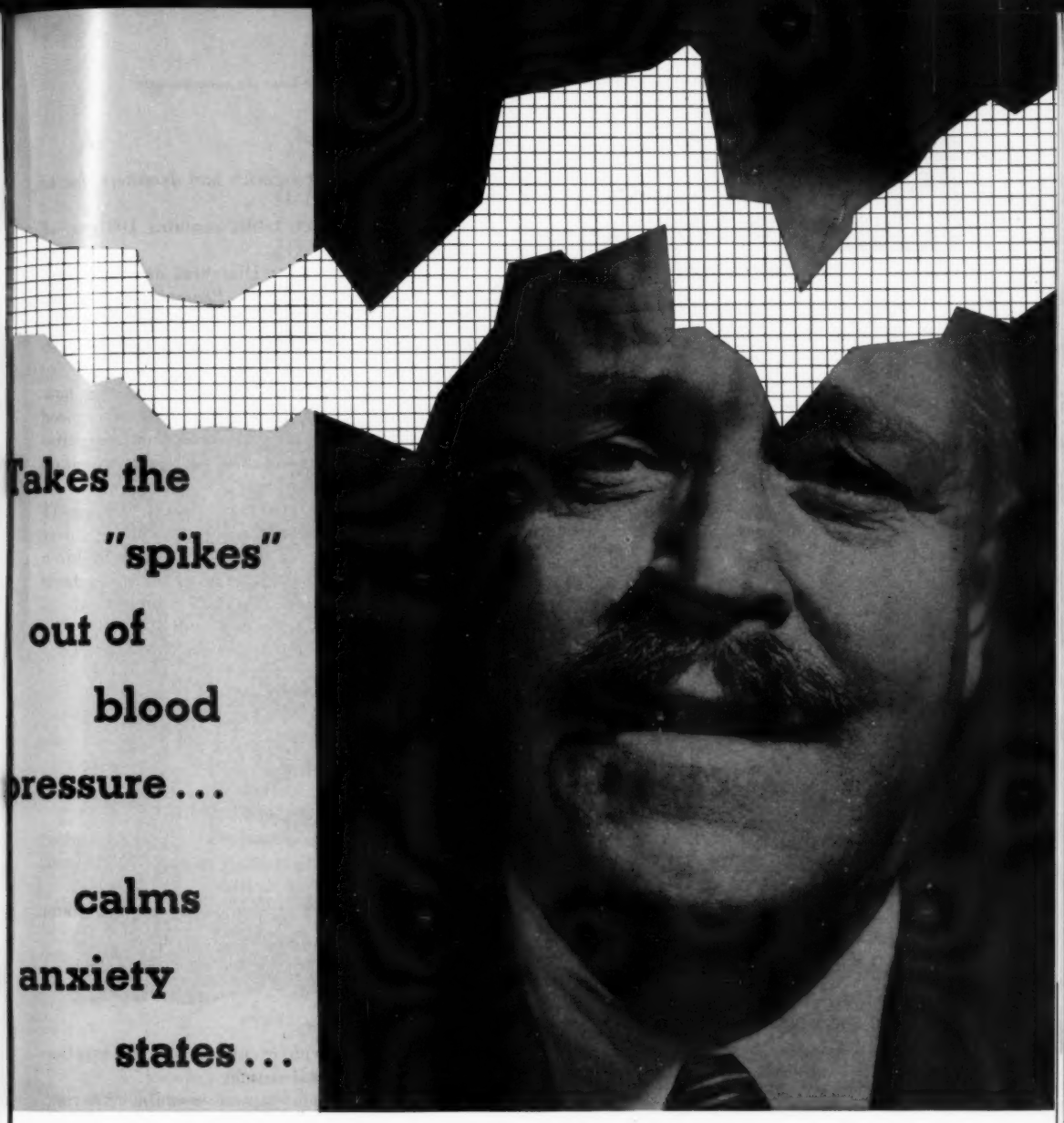
• TESSALON® PERLES

PURPOSE: To control cough reflex.
COMPOSITION: Each perle contains 100 mg. benzontate (Ciba).
INDICATIONS FOR USE: Coughs from colds, bronchial asthma, tuberculosis, emphysema, pneumonia and pleurisy.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

• PANALBA KM GRANULES

PURPOSE: To treat moderately acute, severe or prolonged childhood infections.
COMPOSITION: Each teaspoonful contains a tetracycline (PANMYCIN®) equivalent to 125 mg. of tetracycline hydrochloride, 62.5 mg. of novobiocin calcium (ALBAMYCIN®), and 100 mg. of potassium metaphosphate, in an orange-mint-flavored suspension when mixed with water.
INDICATIONS FOR USE: Pneumococcic, streptococcic, staphylococcic as well as mixed bacterial infections.
DOSAGE AND ADMINISTRATION: 1 teaspoonful per each 15 to 20 lb. body weight per day, given orally in two, three or four doses as practical. The granules are mixed with water before being administered.
PRODUCER: The Upjohn Company, Kalamazoo, Mich.

(Continued on page A-114)



Butiserpine®

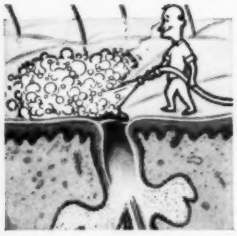
Quiescence is prescribed when you use Butiserpine.

Butisol component acts at once to produce its
l-known quieting "daytime sedation." And the
ll dosage of reserpine gradually builds up its
sion-suppressing effect, without the disturbing
e reactions of larger dosage.

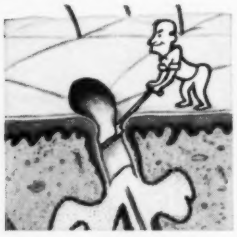
Each tablet or teaspoonful of elixir contains:
BUTISOL SODIUM® 15 mg. (¼ gr.)
Butabarbital Sodium
Reserpine 0.1 mg.
Prestabs® Butiserpine R-A (Repeat Action Tablets)

McNEIL LABORATORIES, INC.
Philadelphia 32, Pa.

IN ACNE Fostex® degreases the skin and helps remove blackheads



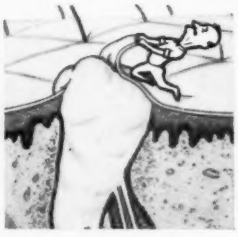
Fostex contains a combination of surface active agents (Sebulytic*) which: Completely emulsify excess oil so that it is quickly washed off the skin.



Penetrate and soften comedones, unblocking the pores and facilitating removal of sebum plugs.

Fostex dries and peels the skin

The Sebulytic base of Fostex dries and promotes peeling of the skin...actions enhanced by the keratolytic effects of micropulverized sulfur and salicylic acid.



*(Sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, sodium dioctyl sulfosuccinate.)

Fostex is easy for your patients to use

Patients stop using soap on affected skin areas. Instead they use Fostex for therapeutic washing of the skin. The Fostex lather is massaged into the skin for 5 minutes—then rinse and dry.

FOSTEX CREAM for therapeutic washing of skin in the initial phase of acne treatment, when maximum degreasing and peeling are desired.

FOSTEX CAKE for maintenance therapy to keep skin dry and substantially free of comedones.

Write for Samples

WESTWOOD *Pharmaceuticals*
Division of Foster-Milburn Co. Buffalo 13, New York

New for Your Armamentarium

• FUROXONE®

PURPOSE: To treat enteritis and dysentery due to bacteria.

COMPOSITION: Each tablet contains 100 mg. of furazolidone.

INDICATIONS FOR USE: Diarrheal disease caused by species of *Salmonella, Proteus* and *Shigella* bacteria; *Escherichia coli* serotypes; staphylococci, and other gram-negative and gram-positive enteric pathogens.

CAUTION: Occasionally, transient headache, nausea or emesis may occur, but can be minimized by reducing the dosage. In rare cases, sensitization is present, but will disappear on termination of treatment.

DOSAGE AND ADMINISTRATION: Adults, 100 mg. (1 tablet) orally four times a day; children over five years old, 50 mg. four times a day; children under five, 5 mg. per kilogram of body weight in four divided doses during a 24 hour period.

HOW SUPPLIED: Bottles of 20 and 100.

PRODUCER: Eaton Laboratories, Norwich, N.Y.

• LOTIOBLANC

PURPOSE: To treat acne.

COMPOSITION: Zinc sulfate and sulfurated potash, with inert stabilizing agents.

DOSAGE AND ADMINISTRATION: Apply morning, noon and night with rotating motion; rub in well.

HOW SUPPLIED: 4 oz. bottles.

PRODUCER: Arnar-Stone Laboratories, Inc., Mount Prospect, Ill.

• MEPROSPAN

PURPOSE: To provide evenly sustained relaxation of mind and skeletal muscle.

COMPOSITION: Each capsule contains 200 mg. meprobamate (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) in the form of coated pellets.

DESCRIPTION: The new form releases the drug continuously for 10 to 12 hours.

INDICATIONS FOR USE: Anxiety and tension states, such as insomnia, premenstrual tension and headaches; skeletal muscle spasm in rheumatic conditions and in certain forms of cerebral palsy.

HOW SUPPLIED: Bottles of 30.

PRODUCER: Wallace Laboratories, New Brunswick, N. J.

(Continued on page A-116)

when they won't take time
to eat what they should...

"THE BOHEMIANS"* BY GERRY GERSTEN

. . . or when a diet goes wrong for *any* reason, what's probably needed first . . . and *most* . . . is the essential B-Complex. That's a good time to remember Sur-Bex with C.

*Coming your way in color next month, Doctor. Watch for them in your mail in June.

a good B-complex . . .

sur-Bex® with C

(Abbott's B-Complex with C)

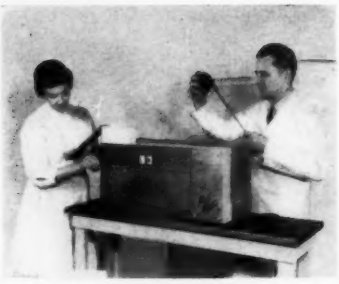
Just one Sur-Bex with C tablet a day represents:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12}	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Desiccated Liver, N. F.	300 mg.
Brewer's Yeast, Dried	150 mg.

As a dietary supplement: 1 or 2 tablets daily
In convalescence: 2 or more tablets daily

Abbott

BOS113



• MEDI-MATIC 16

DESCRIPTION: Specially designed for medical use, this simply operated, self-feeding film processor permits immediate evaluation of negative 16 mm. black and white cineroentgenographic film. The unit features easily interchangeable film transport plastic inserts, a high-speed developer, a rapid fixer, a hypoeliminating agent, and a rinse tank with circulating water. Normal processing speed is 2 ft. per minute, maximal speed is 10 ft. per minute, and film lengths from 1 to 400 ft. may be processed at one time. No dark room is required and fully adjustable speed and temperature controls permit selection of the most favorable processing technics. Packaged developers to be added to the three chemical tanks once a day are available, making prior knowledge of film processing unnecessary; one loading of the 18 oz. tanks is sufficient for the processing of 400 ft. of film. Only two manual operations are required during processing: insertion of film into the entry port with emulsion side down and attachment of its leading edge to a loading spool when the take-up compartment is reached. Drying is carried out by a high-velocity air jet on the emulsion side of the film. Measuring 27 by 16 by 13 in., the unit is finished in stainless steel and plastic.
PRODUCER: Fairchild Camera Instrument Corp., Long Island.

• OL-VITUM-M

PURPOSE: Prevention of vitamin and mineral deficiencies.
COMPOSITION: Each capsule contains seven vitamins, including vitamin B_{12}, and 12 minerals.
DOSAGE AND ADMINISTRATION: 1 capsule daily.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Ives-Cameron Company, Philadelphia.

• PERITRATE® WITH NITROGLYCERIN

PURPOSE: To provide coronary vasodilatation.
COMPOSITION: Each tablet contains 10 mg. pentaerythritol tetranitrate and 0.3 mg. (1/200 gr.) nitroglycerin.
INDICATIONS FOR USE: Angina pectoris attacks.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Warner-Chilcott Laboratories, Morris Plains, N. J.

• PMB-200

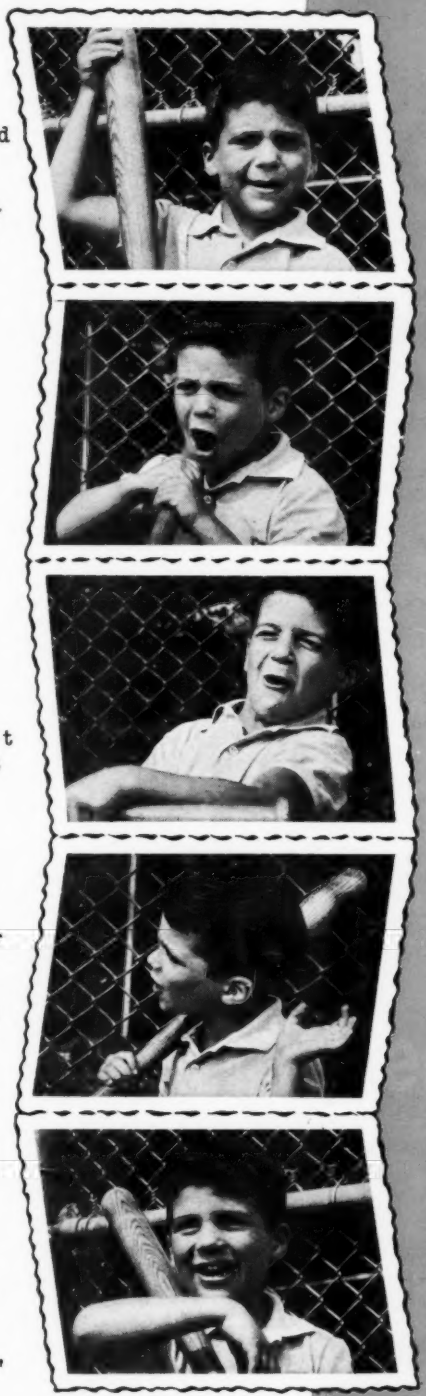
PURPOSE: To provide relief from unusual emotional stress complicating menopause.
COMPOSITION: Each tablet contains 0.4 mg. PREMARIN® and 200 mg. meprobamate. PMB-400 (400 mg. meprobamate) is also available.
HOW SUPPLIED: Bottles of 60 and 500.
PRODUCER: Ayerst Laboratories, New York.

• JACKSON BRONCHOSCOPIC INSTRUMENTS

DESCRIPTION: This group of new instruments includes a bronchoscopic cord with a slip-on feature (top) to assure connection, which can be safely autoclaved, boiled or wiped off with alcohol; and a lens front bronchoscopic lamp (bottom) which projects a forward beam, giving the operator more illumination in the area ahead of the bronchoscope. Two adapters also have been developed; one is designed to connect the slip-on cord with the original light carrier; the other connects the original cord with the new light carrier.
PRODUCER: George P. Pilling & Son Company, Philadelphia.

(Continued on page A-118)

MY DAD— HE HURT HIS BACK REAL BAD



"It happened at work while he was putting oil in something"

"He told Mom his shoulder felt like it was on fire"

"He couldn't swing a bat without hurting"

"But Doctor gave him some nice pills--and the pain went away fast"

"Dad said we'd play ball again tomorrow when he comes home"

AND THE PAIN WENT AWAY FAST

FOR PAIN

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC) **TABLETS**

ACTS FASTER...
usually within 5-15 minutes

LASTS LONGER...
usually for 6 hours or more

MORE THOROUGH RELIEF...
permits uninterrupted sleep through the night

RARELY CONSTIPATES...
excellent for chronic or bedridden patients

and now... **NEW**

Percodan®-Demi

VERSATILE

New "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Available through all pharmacies.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

Literature? Write

Endo **ENDO LABORATORIES**
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

• SUVREN®

PURPOSE: To control emotional stress.
COMPOSITION: Captodiamine hydrochloride.
DESCRIPTION: Avoiding the extremes of emotional response, this nonhypnotic stabilizer calms without inducing drowsiness or sleep and stimulates without causing excitation. It directly relaxes smooth muscle. The drug accelerates reaction time and improves concentration. Since its action is aggregate, self-medication and drug dependence appear to be avoided. It occasionally takes 5 to 10 days before the effects are noted.
INDICATIONS FOR USE: Stress-induced gastrointestinal disorders, mild anxiety, tension, depression, psychogenic asthma, dermatoses of emotional origin, hyperactive children with brain damage, predictable anxiety states, and as an adjunct to tranquilizers in treatment of psychoses.
DOSAGE AND ADMINISTRATION: Adults, 100 mg. three times daily with meals, plus an elective fourth dose at bedtime.
HOW SUPPLIED: 50 and 100 mg. tablets in bottles of 100.
PRODUCER: Ayerst Laboratories, Inc., New York.

• PEDIATRIC PEN-VEE®

PURPOSE: To treat infections caused by penicillin-sensitive organisms.
COMPOSITION: When reconstituted with water, each teaspoonful (5 cc.) contains 250 mg. (400,000 units) penicillin V as benzathine salt, with sodium citrate as buffer, and 0.5 per cent sodium benzoate, 0.014 per cent propylparaben and 0.12 per cent methylparaben as preservatives.
DOSAGE AND ADMINISTRATION: Orally, as needed.
HOW SUPPLIED: As a dry powder, to be reconstituted to 2 fl. oz.
PRODUCER: Wyeth Laboratories, Philadelphia 1.

• INTRAMEDIC POLYETHYLENE TUBING (Three New Sizes)

DESCRIPTION: Electron-sterilized tubing in 12 and 36 in. lengths is now available in sizes for use with 15, 16 and 18 gauge needles, respectively. The tubing is double-packed in an inner glassine envelope and an outer heat-sealed polyethylene envelope, and then irradiated under a 2 million electron V accelerator. Completely sterilized, it may be used from the package.
PRODUCER: Clay-Adams, Inc., New York.

• MICRO-PROJECTION VIEWSCOPE

DESCRIPTION: Featuring a prism lens system that produces brilliant, clearly defined images on a 5 in. diameter Fresnel Lens viewing screen, this instrument will fit any microscope with a monocular tube without special adjustment. The projected image has maximal resolution and uniform sharpness over entire field of view. Any good light source may be used.
PRODUCER: William J. Hacker & Co., Inc., New York.

• RYNATAN® TABULES AND SUSPENSION

PURPOSE: Relief of upper respiratory congestion.
COMPOSITION: Each tabule contains 25 mg. of phenylephrine tannate, 37.5 mg. of prophenpyridamine tannate, and 37.5 mg. of pyrilamine tannate. Each teaspoonful (5 cc.) of suspension contains 5 mg. of phenylephrine tannate, 12.5 mg. of prophenpyridamine tannate, and 12.5 mg. of pyrilamine tannate.
DESCRIPTION: Both the tablets and liquid employ the DURABOND® principle which ensures prolonged effect from a single dose by releasing medication gradually and uniformly over 10 to 12 hours.
INDICATIONS FOR USE: Colds, sinusitis and allergic rhinitis.
DOSAGE AND ADMINISTRATION: Tabules: 1 twice a day. Suspension: adults, 1 to 3 teaspoonfuls twice daily; children six years of age and older, 1 to 2 teaspoonfuls twice daily; children less than six years of age, as directed by physician.
PRODUCER: Irwin, Neisler & Co., Decatur, Ill.

algesic action for

inary tract infections

Bristol

otrex

CAPSULES and SYRUP

THE MEDICAL *Bookman*

► THE YEAR BOOK OF CANCER 1956-1957 Year Book Series

Compiled and edited by Randolph Lee Clark, Jr., M.D., Director and Surgeon-in-Chief, and Russell W. Cumley, Ph.D., Director of Publications, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston. 572 pages with 210 illustrations. 1957, The Year Book Publishers, Inc., Chicago. $7.50.

The appearance in the Year Book Series of a volume devoted exclusively to a review of current literature in the field of cancer should provide welcome and valuable aid to all physicians. A medical problem of unequaled complexity, cancer presents a constant challenge to the physician in many respects, not the least of which is the difficulty of remaining reasonably well informed regarding the changing concepts of its diagnosis and treatment. The overwhelming mass of annual publications in this field, which encompasses all medical and surgical specialties, makes it virtually impossible for even the most avid medical reader to cover the subject adequately. Condensation of this literature into a single volume by recognized authorities in various specialties should be of invaluable aid in disseminating new knowledge about cancer to the medical profession.

The editors and publishers are to be congratulated on the extent to which they have enlisted the editorial assistance of outstanding clinical and research authorities in the field of oncology. The book is notable also for the clarity of its presentation and for the high quality of its photographic and other illustrative material. It should be considered an essential annual addition to the library of all physicians interested in the challenging problem of cancer.

C. M. B.

► CLINICAL HEART DISEASE

By Samuel A. Levine, M.D., Clinical Professor of Medicine, Harvard Medical School, Boston. Ed. 5. 673 pages with 216 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $9.50.

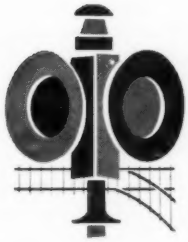
The previous edition of this distinguished text appeared in 1951. In his preface Dr. Levine indicates that the main advance during the last six years has been in heart surgery. The diagnostician nowadays must determine not only whether or not mitral or aortic disease is present, but he must also estimate the degree of stenosis or incompetence and indicate the possibility of corrective surgery. Some advances also have been made in electrocardiography and vectorcardiography. A special chapter entitled "Clinical electrocardiography" has been written by Dr. Harold D. Levine who is now in charge of this work at Peter Bent Brigham Hospital, Boston. The discussions of cardiac dynamics and cardiopulmonary relationships have been expanded.

This work has been recognized as a distinguished contribution to clinical heart disease since the first edition appeared in 1936. No doubt this latest edition will maintain the good repute of previous issues.

M. F.

(Continued on page A-132)

announcing...oral iron under
chelate control for a
SURER HEMATINIC EFFECT



confirmed in J.A.M.A.*

"administration of iron with food...reduce[s] the amount of iron available for hemopoiesis and limit[s] the effectiveness of treatment..."*

"the presentation of iron to the system as a chelate complex [iron choline citrate] permits its administration between meals..."*

CHĒL-IRON
BRAND OF IRON CHOLINE CITRATE† TRADEMARK

CHELATED IRON permits optimal uptake as physiologically required...no iron lost through precipitation...therapy uninterrupted by intolerance

notably effective...exceptionally well tolerated...safest iron to have in the home

■ CHĒL-IRON TABLETS/where iron alone is indicated ■ CHĒL-IRON PEDIATRIC DROPS/can be mixed with milk or formula, will not stain teeth ■ CHĒL-IRON PLUS TABLETS/chelated iron plus B_{12} with intrinsic factor, folic acid, pyridoxine, other essential B vitamins, and C.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685 Apr. 5, 1958.
†U.S. Pat. 2,575,611

Kinney® KINNEY & COMPANY, INC. COLUMBUS, INDIANA

► TREATMENT OF BURNS

By Curtis P. Artz, M.D., Associate Professor of Surgery, University of Mississippi Medical Center, Jackson, Mississippi, and Eric Reiss, M.D., American Cancer Society Scholar and Instructor in Medicine, Washington University School of Medicine, St. Louis. 250 pages with 105 figures. 1957, W. B. Saunders Company, Philadelphia and London. $7.50.

This well-arranged, compact volume on the problem of burns should be favorably received by all medical men who have to deal with this disabling injury. Almost any publication on this subject should be welcome, and especially one of merit such as this.

In the introductory pages, the burn problem is well defined in remarks brief and to the point. The body of the text then is divided into well-organized chapters dealing with general immediate care, fluid-balance problems, local care of the burn wound, surgical closure of the third degree burn by skin grafting, and burns of specific areas. Additional chapters deal with infection, metabolic problems, special types of burns, anesthesia, nursing care, certain aspects of the attending emotional problems, complications, therapy, and management of burns in disaster.

Each chapter has a bibliography which, though small, seems adequate. The general orientation and the printing layout make for easy reading and assimilation of the information presented by the authors. The discussion of proper usage of the exposure method and the occlusive-dressing method in initial care of the burn wound is unbiased, brief and logical. The same comment would hold for the authors' discussion of the methods of obtaining skin grafts.

Unfortunately, the paragraphs devoted to burns of the hands and also to electric burns are quite brief, although well done.

The chapter dealing with infection of the burn wound is satisfactory. Some, including the reviewer, would take exception to the use of local antibiotics on the burn wound and perhaps would rely on saline baths and general systemic use of indicated antibiotics. However, the authors very frankly list the disadvantages of local antibiotic therapy.

It seems apparent that this excellent volume should be in the hands of all doctors of medicine, especially if there is a nuclear war.

P. J. K.

► HEART DISEASE AND PREGNANCY
Physiology and Management

By C. Sidney Burwell, M.D., Samuel A. Levine Professor of Medicine, and James Metcalfe, M.D., Associate in Medicine, Harvard University, Boston. 338 pages with 44 illustrations. 1958, Little, Brown & Company, Boston. $10.00.

The authors have shown unusual ability in cramming a vast amount of information into a small volume and making it read like a novel. The text is divided into three parts: a discussion of physiologic changes in pregnancy, the physiodynamic variations in heart disease, and a terse discussion of various types of cardiac pathology as they pertain to the pregnant woman.

The text is profusely illustrated with charts and diagrams. The authors, by their direct observation of hundreds of patients at the Boston Lying-In Hospital and by their ability to obtain extensive laboratory studies, have accomplished a most outstanding work. This book should certainly be read by every obstetrician and by physicians who treat pregnant patients.

E. A. B.

► ANTIBIOTICS ANNUAL 1957-1958

Edited by Henry Welch and Felix Marti-Ibanez. 1,070 pages. 1958, Medical Encyclopedia, Inc., New York. $12.00.

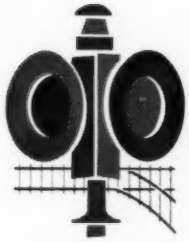
This book represents a compilation of the papers prepared for the Fifth Annual Symposium on Antibiotics. The symposium is held in the fall of each year, and much of the current research concerning antibiotics is presented at that time. Publication of this book follows within a few months.

Many of the papers included are of a technical nature, and the review is of primary interest to those engaged in the development and investigation of antibiotics. There are textbooks dealing with antibiotics which are more suitable for use by the practicing physician, although he could use this volume for more specific data concerning the various antibiotics. As I have indicated, it is a complete and excellent reference text. Certainly it should be included in any general medical library.

W. E. W.

(Continued on page A-134)

announcing...oral iron under chelate control for VIRTUAL FREEDOM FROM G.I. INTOLERANCE



confirmed in J.A.M.A.*

"One of the major difficulties associated with iron therapy is that of the occurrence of gastrointestinal disturbances..."*

"iron choline citrate, a chelated form of iron, possesses outstanding qualities in terms of freedom from undesirable gastrointestinal effects."*

CHĒL-IRON

BRAND OF IRON CHOLINE CITRATE† TRADEMARK

CHELATED IRON...remains in solution...no irritating ionization or precipitation...acceptable even to peptic ulcer patients...can be taken on an empty stomach

exceptionally well tolerated...notably effective...safest iron to have in the home

■ CHĒL-IRON TABLETS/three tablets supply 120 mg. elemental iron ■ CHĒL-IRON PEDIATRIC DROPS/each cc. supplies 16 mg. elemental iron in a flavored, nonalcoholic vehicle ■ CHĒL-IRON PLUS TABLETS/three tablets supply 72 mg. elemental iron plus B_{12} with intrinsic factor, folic acid, pyridoxine, other essential B vitamins, and C.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.
†U. S. Pat. 2,575,611

Kinney® KINNEY & COMPANY, INC. COLUMBUS, INDIANA

► UNDERSTANDING YOUR PATIENT

Edited by Samuel Liebman, M.D., Medical Director, North Shore Hospital, Winnetka, Illinois, with 10 contributors. 170 pages. 1957, J. B. Lippincott Company, Philadelphia and Montreal. $5.00.

Each year the North Shore Hospital in Winnetka, Illinois, sponsors a lecture series in the field of psychiatry. This book is based on the seventh annual series titled "The medical practitioner's contributions toward healthy emotional development—the physician as a counselor."

The nine chapters, each by a different contributor who is very well known in the field of child and adult psychiatry, more or less relate to the general topic. After the early chapters on emotional development, including infancy, school-age and teen-age children, and emotional conflicts of adult life, come chapters on premarital and marital counseling and problems relating to grandparents. There is also a discussion of "Psychologic preparation of the individual for medical and surgical care." The individual topics include a liberal number of illustrative cases.

The authors have written in a simple, lucid fashion, in terms easily comprehensible to those for whom the book is intended, viz., medical students, nurses, general practitioners and, in general, nonpsychiatrists in the medical field.

E. M. L.

► OPERATIVE OBSTETRICS

By R. Gordon Douglas, M.D., Professor of Obstetrics and Gynecology, Cornell University Medical College, New York, and William B. Stromme, M.D., Attending Obstetrician and Gynecologist, Northwestern and Fairview Hospitals, Minneapolis. 735 pages, illustrated. 1957, Appleton-Century-Crofts, Inc., New York. $20.00.

A major contribution to obstetrics, this excellent text is the first American book published in more than 80 years that has dealt exclusively with the operative phase of obstetrics. It presents a vast amount of clinically practical information that can be found in no other book. The text is clearly written, complete, and adequately detailed. There is a wealth of excellent illustrations, which often include both photographs and diagrams of each important step of a surgical procedure. In addition to thorough descriptions of operative technics, there are authoritative discussions of the rationale of the various procedures, their indications, and their contraindications. These discussions are based on the extensive experience of the authors and the New York Lying-In Hospital, as well as on knowledge drawn from the pertinent world literature.

The first chapters present valuable and basic information in the fields of anatomy, preoperative and operative care, and anesthesia and analgesia. Induction of labor and the operative management of ectopic pregnancy and abortion are then discussed. An exceptionally fine chapter on forceps operations contains more than 200 helpful illustrations. Thorough discussions and detailed descriptions are given on cesarean section, version, breech extraction, conversion, embryotomy, episiotomy and repair of obstetric trauma, and other operations on the genital tract. The final chapters very adequately cover postoperative care, management of postoperative complications, and surgery outside the generative tract for the obstetric patient.

L. A. A.

► YEAR BOOK OF DRUG THERAPY 1957-1958 Year Book Series

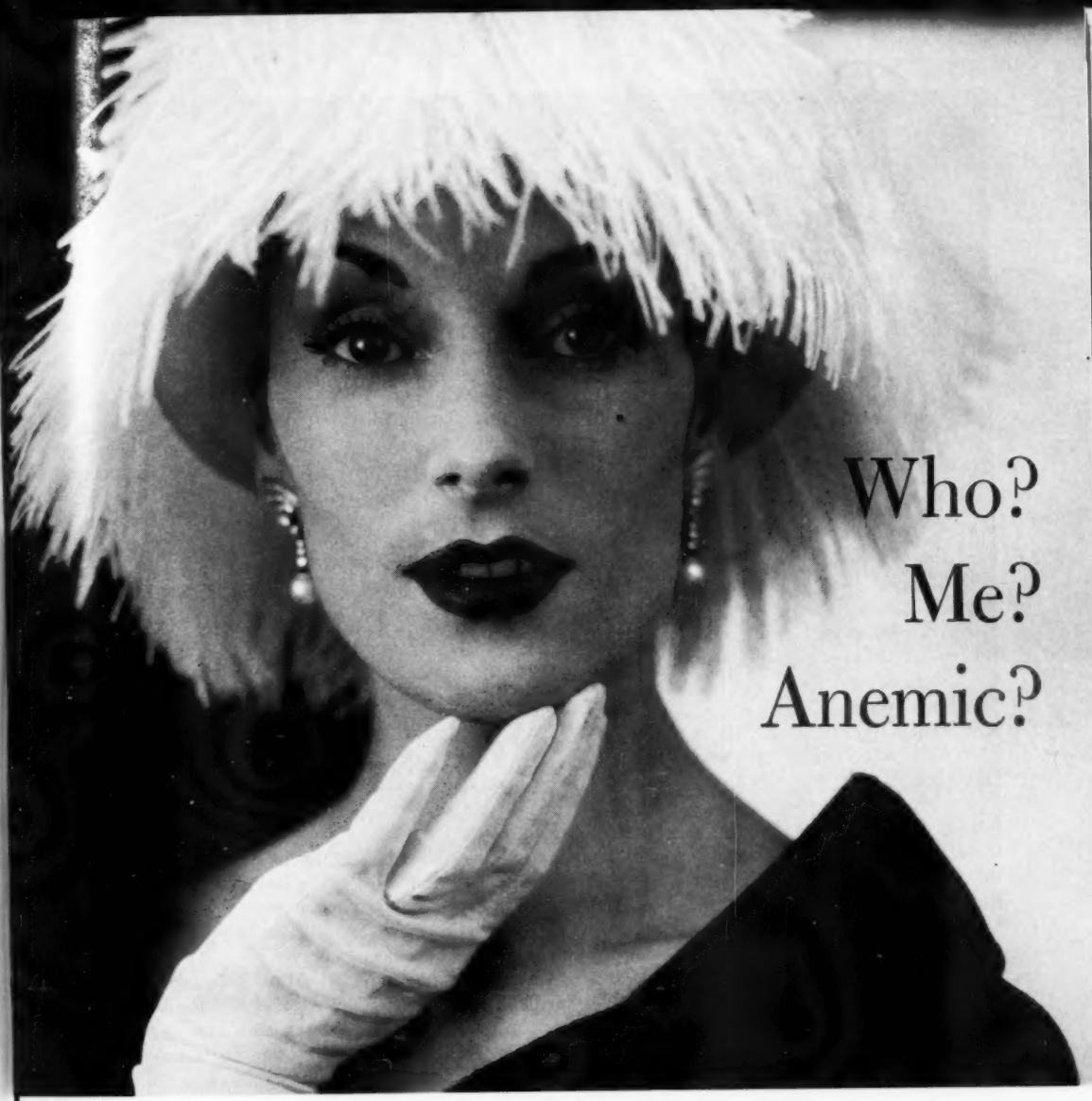
Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. 518 pages, illustrated. 1958, The Year Book Publishers, Inc., Chicago. $7.50.

Dr. Beckman has done an excellent job in selecting the drugs to be included in this volume and in describing their usage. I believe it to be a trying task for anyone, even the physician-pharmacologist, to select important contributions in the field of drug therapy to place in one volume.

None of the abstracts are overly lengthy, and the footnote references allow the reader to refer to the original presentation for a more thorough investigation of each subject discussed.

This is an excellent reference for general physicians and internists. The editorial by Dr. Beckman on pages 5 and 6 gives us much food for thought in this present-day multitudinous production and duplication of drugs by various manufacturers. This editorial alone is worth the price of the book, and by all means should be thoroughly read by all pharmaceutical manufacturers in this country.

I. P. F.



FALVIN Capsules are fully efficient not only in patients with severe anemias, but also in the wide range of patients with marginal and incipient deficiencies—convalescents, geriatric patients, adolescents, and the many listless, easily-fatigued individuals. FALVIN with AUTRINIC consistently enhances absorption of the Vitamin B_{12} component. As a result of this across-the-board effectiveness, FALVIN is the oral hematinic you can depend on completely *whenever a hematinic is indicated!*

Dosage: One capsule twice daily.

Each FALVIN capsule contains:

*Autrinic** Intrinsic Factor Concentrate with Vitamin B_{12}	1 U.S.P. Oral Unit
Ferrous Sulfate Exsiccated	300 mg.
Ascorbic Acid (C)	75 mg.
Folic Acid	1 mg.

*Reg. U. S. Pat. Off.

Lederle

for the common anemias in their many phases

FALVIN*

Hematinic Lederle

with AUTRINIC*

Intrinsic Factor Concentrate with B_{12}

LEDERLE LABORATORIES
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AMERICAN CYANAMID COMPANY
Pearl River, New York

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Feb. 24—Z. W. H. returned from her honeymoon to a day of hard work.

Feb. 25—By plane to Melbourne, Florida, reading en route "Below the Salt" by Costain, and found it on the boring side. Met by Collins Ervin as we arrived in a cold, penetrating rain and went to the Bahama Beach Club to dine and thereafter to view television.

Feb. 26—In the morning at the scrivening. In the afternoon to visit the hospital which was built with 23 beds and now houses 63 patients. Thereafter to cocktails at the home of Dr. T. J. Kaminski and met the medicos from roundabout, including J. M. Gayden, J. A. Sewell, Bechtel, Von Meysenburg, and many more. Next to the Eau Gallie Civic Center where assembled a thousand citizens to dine and to hear of the need for a new hospital, the area population having risen from 6000 to 40,000 because of the Army's missile program.

Feb. 27—By the early plane to Miami, meeting Dr. Russell A. Williams, formerly of Abbott's, and chatted with him of the old days in Chicago and of the Cancer Research and Cytology Center. Then to the Americana for a restful afternoon and a most gracious reception by Al Tisch and his hospitable wife. In the evening with Charles Haney and Israel Benjamin of Salisbury, Maryland, and all the ladies to dine at the Lighthouse.

Feb. 28—Resting late and for lunch came my sister Jennie Rauh and my sister-in-law Hilda and we played gin so that nobody won. In the evening playing bingo, and Mistress Pepys excelled.

Mar. 1—Down to Lincoln Road to visit the shops. In the evening to walk in the beautiful gardens and around the pool and met the Purvins, Alschulers who had been to Hialeah, Axelrods, Dr. L. Sauer, Wolfsohn of Boston, and Sawtelle of Long Island.

Mar. 2—By the Golden Falcon on Eastern Airlines flying luxuriously to New York. En route read a paperback mystery by McDonald who seems to turn out a few each month. Read also a new mystery by Masur called "The Long Gamble," and this was sharp and modern. In the evening to dine at the Mayes' where Amalia had made wonderful *kropfen* which is a doughnut with jelly inside.

Mar. 3—A day of conferences at Doubleday with Runyon and Joe Marks, and then all through noon with Paul Robinson working on a new periodical. Peter Warren came thereafter to discuss the great expansion of *Excerpta Medica;* then Mr. Otto Frank and his lady to plan for the Anne Frank Foundation, and to the LaGuardia field for the flight to Chicago.

Mar. 4—Again a day of intensive correspondence and at night to the Hilton where the Lyric Opera held its first membership meeting, and heard fine reports from Spacek, Stathas, Glore and Carol Fox. Then home and read a psychoanalyst's report by Dr. Harold Greenwald called "Call Girl."

Mar. 5—At the desk and in between read "Mandingo," a realistic novel of a slave farm in Alabama before the Civil War, overloaded with sex, but it must have been as the author describes it. Also this day to luncheon at the Hall of Fame with Fischer of Kiel and nine Frenchmen en route to Los Angeles, and after that to a jam-packed session of the Chicago Medical Society's Midwinter Conference.

Mar. 6—In the afternoon to the airport to greet Dr. and Mrs. Marino-Zuco and the Del Tortos from Rome. Later took them to the Edgewater Beach, then to view the Hall of Fame for Surgery and thereafter to Camelia House at the Drake for a wonderful dinner with Max Thorek, the Italian consul Profili and his lady, and also the public relations attaché Borselli.

Mar. 7—Early with the guests to view the Cook County Hospital and saw much new construction in radiology and admitting departments. Viewed also the surgery, and then to the Hektoen Institute where research on leukemia and congenital heart disease is especially noteworthy. Next to the Tavern Club where were Lewin, Hauser, Sam Hoffman, Friedell, Marino-Zuco, Del Torto and old Pepys. Next to the University of Chicago, meeting Coggeshall, LeRoy, Ray Brown and Carpenter, and with the professor of orthopedics from Osaka in Japan to view Hatcher's service and the research in the Gold-

(Continued on page A-176)

HYPERTENSIVE...yet controlled
with safer combination therapy

"objective relief...gratifying"

Rauvera—the combination of alseroxylon and alkavervir—is much more effective than either drug alone. This combination produces "no postural hypotension, no organ toxicity, and no sensitization reactions. Tolerance does not develop on prolonged administration...hypotensive action is steady and prolonged and persists over the entire twenty-four hours.[1]" Rauvera therapy can be continued over long periods of time.

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Alseroxylon and alkavervir "when combined produce mutual reinforcement so that...more severe cases respond," yet "side effects are minimal."[2] Most patients feel better, are less tired and are free from headaches.[3] Anxiety and tension are relieved...pulse rate slowed...such symptoms as "heart consciousness," tinnitus, vertigo, giddiness and insomnia disappear rapidly —leaving a calm and relaxed patient.

RAUVERA®

Each scored tablet of Rauvera contains 1 mg. purified Rauwolfia serpentina alkaloids (alseroxylon) and 3 mg. alkavervir, biologically standardized.

1. Bendig, A.: New York State J. M. 56:2523, 1956. 2. La Barbera, J. F.: Med. Rec. and Ann. 50:242, 1956. 3. Gilchrist, A. R.: Brit. M. J. No. II:1011, 1956.

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blatt Foundation. Thereafter to the Museum of Science and Industry where Major Lohr made all welcome. In the evening with all the ladies to the Boulevard Room at the Hilton where the Ice Show was terrific and the food terrible.

Mar. 8—With our guests to the airport, wishing them "*Bon Aviation.*" In the afternoon saw Indiana, vastly superior, defeat Michigan State in basketball. In the evening to the Winstons' for a grand dinner and sat between Mmes. Kirsner and Cornbleet, delightfully interesting, especially the saga of Minnie's battle with a traffic cop.

Mar. 9—Reading Jack Kerouac's "The Subterraneans," which is stream of consciousness and degenerate. In the afternoon to Howard Willett's for the opening of the Easter Seal campaign and met the stars of the Chicago cast of "My Fair Lady" and Sally Joy Brown of the *Chicago Tribune* and all the good people who care for the handicapped. Then with Walter Krafft and his lady to eat hamburgers at the International Club and to talk.

Mar. 10—At the desk with a visit from Henry Legler to talk of antiseptics, and read "Angry Harvest," a story of Poland during the German invasion written by two prisoners, Herman Field and Stanislaw Mierzenski.

Mar. 11—All this day engaged with the medical periodicals, and in the evening observing television.

Mar. 12—At noon with Drs. Colwell, Abrams, Turner, Graning, Rosenblum, Wright Adams and deBoer to work on the home service plan for Cook County Hospital. In the evening with the Scuderis at a showing of Italian fashions for the benefit of the Polio Foundation.

Mar. 13—In the evening to hear Bruno Walter, now 82 years old, and the Chicago Symphony Orchestra in Schubert's "Unfinished Symphony" and Mozart's "Requiem," for which there were four fine artists and a new chorus.

Mar. 14—Early to consult with Scheer who gives good advice on taxes and then to Armour to confer with Fred Gibbs and Conquest on infantile myoclonus which seems to yield to ACTH. At night to the home of Judge Brown and his lady, where also were Metzger of Ruthrauff-Ryan, Sensibar, who literally moves mountains all over the world, Walter Krafft, Fisher and all the ladies, for a wonderful evening.

Mar. 15—Now entertaining Rosemary and Amy Louise, and took them to the Museum of Science and Industry which is an absorbing adventure for every adult and every child. In the evening to the Quadrangle Club with Joe and Minnie Kirsner and sat with the teachers of French and renewed my acquaintanceship with many of the faculty. So then to a revue written by Bob Pollak and Robert Ashenhurst called "The Sky's No Limit," full of pointed skits, clever lyrics, intriguing music and some gorgeous satires on pretentious learning.

Mar. 16—Attending to the tiny guests and read a Holly Roth mystery about a family somewhat like the Barrymores, called "The Crimson in the Purple." In the afternoon to Dorfmans' new apartment which overlooks Jackson Park and La Rabida and that is certainly keeping close to your work. At night came Justin and Danny who waits for the mumps to which Amy exposed him.

Mar. 17—St. Patrick's Day and Danny has the mumps. In *The New York Times* read many letters about brevity in letters. Later played at gin with my brother Albert, who always manages to stop when he is ahead.

Mar. 18—At the desk reading the foreign periodicals. At noon come A. Willinsky of Toronto with his lady to lunch and to tell of the surgical meeting in Los Angeles. Thereafter to the Nettlehorst School where Barbara Friedell had organized a great health show, and meeting there the many fine ladies who conduct these affairs in Chicago. At night with the Harry Zelzers and Kirsners to dine at the Tavern and afterward to the newly refurbished Eighth Street Theater.

Mar. 19—At the desk and read "Madison Ave. U.S.A." with its startling facts about the advertising industry and also a few rumors instead of facts. In the afternoon, driving with Charles Haney to La Grange. First to the Community General Hospital which is one of the finest hundred bed hospitals I have ever seen, and the administrator Clifford S. Johnson, trained at Hopkins and in the Navy, keeps it in shipshape condition. Here met Dr. Paul H. Van Verst who is chief of staff and Diane Croll, pathologist. Thereafter to speak in the Y.M.C.A. in the interest of raising $1,000,000, and most likely they will do it soon for this is a proud community.

Mar. 20—For conference came Dr. Edmund Jacobson who

(Continued on page A-180)

Documentary Case History . . .

Hypertension controlled for four years with Serpasil®

(reserpine CIBA)

K. C., a 67-year-old retired shirt manufacturer, had a 16-year history of hypertension, was troubled by recurrent dizzy spells and headaches. "I'd get several attacks a day. . . . Usually I'd go into the bedroom and lie down." Serpasil therapy was started four years ago, effecting a gradual reduction of the patient's initial blood pressure of 220/120 mm. to the present 140/80. Now well and asymptomatic, ". . . I'm able to go to matinees and see some of the TV shows."

SUPPLIED: TABLETS, 4 mg. (scored), 2 mg. (scored), 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg.

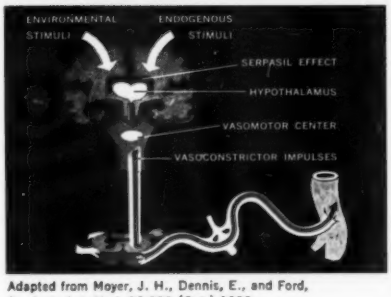
ELIXIRS, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

PARENTERAL SOLUTION: *Ampuls*, 2 ml., 2.5 mg. Serpasil per ml. *Multiple-dose Vials*, 10 ml., 2.5 mg. Serpasil per ml.

Hypertension controlled through

SYMPATHETIC REGULATION

Serpasil shields the psychic and somatic reaction centers from emotional and environmental stress stimuli, thereby inhibiting the discharge of vasoconstrictive impulses through the sympathetic nerves.



Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

CIBA SUMMIT, N. J. 2/2595HK

has established a foundation to teach relaxation for the control of tension. In the afternoon to Milwaukee reading Mark G. Field's book on "Doctor and Patient in Soviet Russia."

In Milwaukee greeted by Dr. Mary Hall and Miss Lausdon. With them to Children's Hospital for a fine buffet dinner of German delicatessen, and here were Drs. Peterman, Peterson, Wynn and Blount and many of the occupational and physical therapists. Then to speak to a hundred of the auxiliary professions at Marquette University, telling them of medical writing.

Mar. 21—With Morris Gordon, working out a campaign for the City of Hope, and talked with Bob Kleckner and Coggeshall about the sad state of the coroner's office in Cook County. In the evening came Lucile and Richard Finnegan, Ruth Corcoran, Konrad Ragoczy from Copenhagen, Georgianna Richards, Mrs. Meyer, Justin and Ann for a fine evening of dining and conversing and watched Logart battle Akin in Madison Square Garden.

Mar. 22—This day reading "Wine of Life" by Gorham, a fictional life of Balzac, a most rewarding experience in literary enjoyment, and resolved to read again "The Physiology of Marriage." So called Pepi Schildkraut in Beverly Hills to congratulate him on his birthday and found him well and happy.

Mar. 23—At my work, and in the evening to a dinner of the Julian Levinson Foundation for the Mentally Retarded where Mrs. Herman Jacobson spoke well of the work of the Foundation and old Pepys told of new research. Here also talked with Dan Ryan of the desire to improve the coroner's office.

Mar. 24—At the desk and read "Patients and Doctors" by Kenneth Walker, greatly esteemed British surgeon.

In the evening by plane to Quincy, Illinois, on the majestic Mississippi. Here Harold Swanberg came to greet me and at his home meeting his gracious lady, and there came also my friend Ralph McReynolds of medical school days, Warner Pearce, Guy Tourney, president of the Adams County Medical Society, and Givi Gabliani, and after an hour of reminiscing off to bed.

Mar. 25—Early awake and first to the gorgeous new high school to speak to a thousand students in the fine assembly hall. With Superintendent Brockton viewing the wonderful facilities. At noon to speak for a joint session of Kiwanis and Rotary and saw a psychiatrist, Rylander, inducted into Rotary with the Kiwanians shouting that they did not need a psychiatrist. Next to speak for a convocation in Notre Dame Academy, and to interviews at two television stations. Thereafter to a dinner in the fine country club and to speak of "The Promise of Medicine" to 800 citizens, and stood in line in a reception. By this time the larynx began to demonstrate resistance, so went back to listen to the Robinson-Basilio fracas.

Mar. 26—Early awake with no voice left whatever, so Mistress Pepys at the airport said I could go no farther. En route home read a paperback by John McPartland, warmer than Mickey Spillane and full of physiology. All day working with a whisper according to Sam Pearlman's instruction. In the evening with Mistress Pepys and Belle to see the opening of the movies' "South Pacific" for the benefit of Boy's Town of Italy, meeting again Madame Spyros Skouras and Consul Profili and many more.

Mar. 27—At the desk still whispering. So edited papers on viruses and on history. Read also "Practice to Deceive," a stylish mystery by the Lockridges. In the night to hear Fritz Reiner conduct Haydn, Ravel and Wagner, three amazingly different composers, and agreed with Mrs. Cornbleet that Ravel is remarkably like Gershwin.

Mar. 28—All day at the desk and in the evening to the magnificent home of Ed Weiss, advertising tycoon, for a dinner with all the trimmings. Here also Gita Gradova and her spouse Dr. Maurice Cottle.

Mar. 29—Reading another mystery by Holly Roth, "Shadow of a Lady," a fine story with sustained suspense. Most of the time engaged in editing the first volume of historical lectures from the Hall of Fame for Surgery.

Mar. 30—Still editing and Sam Mantel came for legal and mathematical conferences, old Pepys doing well. Then with my brother Albert and Belle to Phil Schmidt's for perch which are of the best.

Mar. 31—At noon to the Standard Club for luncheon with Sid Sideman, the orthopod, and also came Mistress Pepys and Walter Kahoe. Thereafter a conference with Noah Fabricant on our literary endeavors. At night to the eightieth birthday party of Ben Samuels, prexy for many years of Yellow Cab, and it was a joyous occasion.